```
Connecting via Winsock to STN


Welcome to STN International!  Enter x:x

LOGINID:ssptamxg1614

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  JAN 08   CHEMLIST enhanced with New Zealand Inventory of Chemicals
 NEWS  3  JAN 16   CA/CAplus Company Name Thesaurus enhanced and reloaded
 NEWS  4  JAN 16   IPC version 2007.01 thesaurus available on STN
 NEWS  5  JAN 16   WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data
 NEWS  6  JAN 22   CA/CAplus updated with revised CAS roles
 NEWS  7  JAN 22   CA/CAplus enhanced with patent applications from India
 NEWS  8  JAN 29   PHAR reloaded with new search and display fields
 NEWS  9  JAN 29   CAS Registry Number crossover limit increased to 300,000 in
                   multiple databases
 NEWS 10  FEB 15   PATDPASPC enhanced with Drug Approval numbers
 NEWS 11  FEB 15   RUSSIAPAT enhanced with pre-1994 records
 NEWS 12  FEB 23   KOREAPAT enhanced with IPC 8 features and functionality
 NEWS 13  FEB 26   MEDLINE reloaded with enhancements
 NEWS 14  FEB 26   EMBASE enhanced with Clinical Trial Number field
 NEWS 15  FEB 26   TOXCENTER enhanced with reloaded MEDLINE
 NEWS 16  FEB 26   IFICDB/IFIPAT/IFIUDB reloaded with enhancements
 NEWS 17  FEB 26   CAS Registry Number crossover limit increased from 10,000
                   to 300,000 in multiple databases
 NEWS 18  MAR 15   WPIDS/WPIX enhanced with new FRAGHITSTR display format
 NEWS 19  MAR 16   CASREACT coverage extended
 NEWS 20  MAR 20   MARPAT now updated daily
 NEWS 21  MAR 22   LWPI reloaded
 NEWS 22  MAR 30   RDISCLOSURE reloaded with enhancements
 NEWS 23  MAR 30   INPADOCDB will replace INPADOC on STN
 NEWS 24  APR 02   JICST-EPLUS removed from database clusters and STN

 NEWS EXPRESS  NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS LOGIN    Welcome Banner and News Items
 NEWS IPC8     For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN Customer
  agreement.  Please note that this agreement limits use to scientific
  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 07:38:47 ON 20 APR 2007

=> file reg
```

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.84	0.84

FILE 'REGISTRY' ENTERED AT 07:41:19 ON 20 APR 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 18 APR 2007 HIGHEST RN 930838-51-0
DICTIONARY FILE UPDATES: 18 APR 2007 HIGHEST RN 930838-51-0

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

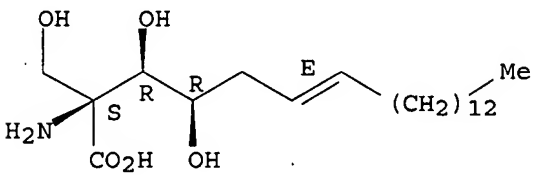
Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

```
=> s myriocin
L1            3 MYRIOCIN

=> d 1-3

L1   ANSWER 1 OF 3  REGISTRY  COPYRIGHT 2007 ACS on STN
RN   156556-20-6  REGISTRY
ED   Entered STN:  26 Jul 1994
CN   6-Eicosenoic acid, 2-amino-3,4-dihydroxy-2-(hydroxymethyl)-,
     (2S,3R,4R,6E)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   6-Eicosenoic acid, 2-amino-3,4-dihydroxy-2-(hydroxymethyl)-,
     [2S-(2R*,3S*,4S*,6E)]-
OTHER NAMES:
CN   14-Deoxomyriocin
FS   STEREOSEARCH
MF   C21 H41 N O5
SR   CA
LC   STN Files:   CA, CAPLUS, CASREACT, TOXCENTER
```

Absolute stereochemistry.
Double bond geometry as shown.

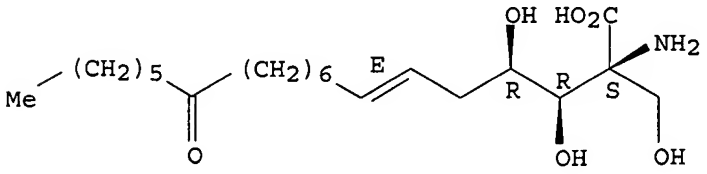


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2007 ACS on STN
RN 35891-70-4 REGISTRY
ED Entered STN: 16 Nov 1984
CN 6-Eicosenoic acid, 2-amino-3,4-dihydroxy-2-(hydroxymethyl)-14-oxo-, (2S,3R,4R,6E)- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 6-Eicosenoic acid, 2-amino-3,4-dihydroxy-2-(hydroxymethyl)-14-oxo-, [2S-(2R*,3S*,4S*,6E)]-
OTHER NAMES:
CN (+)-Myriocin
CN (2S,3R,4R)-(E)-2-Amino-3,4-dihydroxy-2-hydroxymethyl-14-oxoeicos-6-enoic acid
CN ISP-I
CN Myriocin
CN Thermozymocidin
FS STEREOSEARCH
DR 36564-60-0, 37836-36-5
MF C21 H39 N O6
LC STN Files: AGRICOLA, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSDRUGNEWS, IMSRESEARCH, MEDLINE, NAPRALERT, PHAR, PROMT, PROUSDDR, RTECS*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.
Double bond geometry as shown.

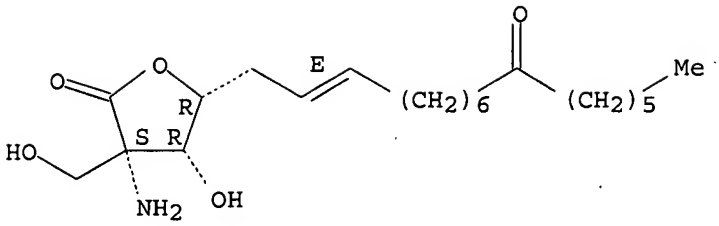


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

106 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
107 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2007 ACS on STN
RN 35891-69-1 REGISTRY
ED Entered STN: 16 Nov 1984
CN 2(3H)-Furanone, 3-aminodihydro-4-hydroxy-3-(hydroxymethyl)-5-[(2E)-10-oxo-2-hexadecenyl]-, (3S,4R,5R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2(3H)-Furanone, 3-aminodihydro-4-hydroxy-3-(hydroxymethyl)-5-(10-oxo-2-hexadecenyl)-, [3S-[3α,4α,5α(E)]]-
OTHER NAMES:
CN Anhydromyriocin
CN Myriocin, anhydro-
FS STEREOSEARCH
MF C21 H37 N O5
CI COM
LC STN Files: BEILSTEIN*, CA, CAPLUS, RTECS*, TOXCENTER
(*File contains numerically searchable property data)

Absolute stereochemistry.
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

8 REFERENCES IN FILE CA (1907 TO DATE)
8 REFERENCES IN FILE CAPLUS (1907 TO DATE)

```
=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      11.25      12.09

FILE 'CAPLUS' ENTERED AT 07:41:58 ON 20 APR 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)
```



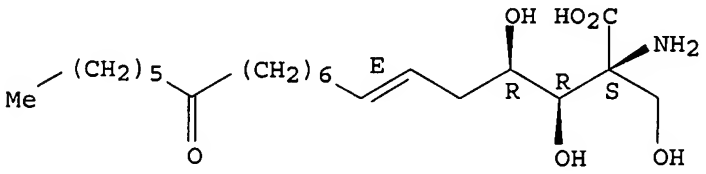
```
FILE COVERS 1907 - 20 Apr 2007  VOL 146 ISS 18
FILE LAST UPDATED: 19 Apr 2007  (20070419/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html

=> s 35891-70-4/rn
           107 35891-70-4
             4 35891-70-4D
L2           103 35891-70-4/RN
                 (35891-70-4 (NOTL) 35891-70-4D )

=> s l2 and hepatocyte
         48497 HEPATOCYTE
L3           3 L2 AND HEPATOCYTE

=> d 1-3 bib abs hitstr

L3   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
AN   2005:823310  CAPLUS
DN   143:206468
TI   Ceramide de novo synthesis-based methods for modulation of mature SREBP,
     and related therapeutic methods and articles of manufacture
IN   Worgall, Tilla S.; Deckelbaum, Richard J.
PA   USA
```

SO U.S. Pat. Appl. Publ., 45 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2005182020	A1	20050818	US 2003-712684	20031114
PRAI US 2003-712684		20031114		

AB A method is described for decreasing the amount of mature SREBP (mSREBP) in a cell characterized by an elevated level of mSREBP comprising contacting the cell with an agent that specifically inhibits de novo synthesis of ceramide in the cell, thereby decreasing the amount of mSREBP in the cell. Also described are related therapeutic methods and articles of manufacture
IT 35891-70-4, Myriocin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ceramide de novo synthesis-based methods for modulation of mature SREBP)
RN 35891-70-4 CAPLUS
CN 6-Eicosenoic acid, 2-amino-3,4-dihydroxy-2-(hydroxymethyl)-14-oxo-, (2S,3R,4R,6E)- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L3 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:326221 CAPLUS
DN 142:458423
TI Myriocin prevents fumonisin B1-induced sphingoid base accumulation in mice liver without ameliorating hepatotoxicity
AU He, Quanren; Riley, Ronald T.; Sharma, Raghubir P.
CS Department of Physiology and Pharmacology, College of Veterinary Medicine, University of Georgia, Athens, GA, 30602-7389, USA
SO Food and Chemical Toxicology (2005), 43(6), 969-979
CODEN: FCTOD7; ISSN: 0278-6915
PB Elsevier B.V.
DT Journal
LA English
AB Fumonisin B1 (FB1), a mycotoxin produced by Fusarium verticillioides present on corn and corn-based products, causes species- and organ-specific diseases. The hepatotoxic effects of FB1 in mice were closely correlated with the accumulation of free sphinganine, a marker for ceramide synthase inhibition, and reduced biosynthesis of more complex sphingolipids. It was shown that FB1 modulates expression of many cell signaling factors. In the current study the authors used myriocin, a specific inhibitor of serine palmitoyltransferase, to investigate the role of free sphinganine accumulation in FB1-induced hepatotoxicity and increased expression of selected signaling genes in BALB/c mice. The mice were pretreated daily with i.p. injection of 1.0 mg/kg myriocin 30 min before s.c. injections of 2.25 mg/kg of FB1 for 3 days. Results showed that myriocin alone was not hepatotoxic and the combination of myriocin plus FB1 completely prevented the FB1-induced elevation of hepatic free sphinganine and prevented the FB1-induced induction of selected cell signaling genes, suggesting that accumulation of free sphinganine and/or its metabolites contribute to the FB1-modulation of the cell signaling

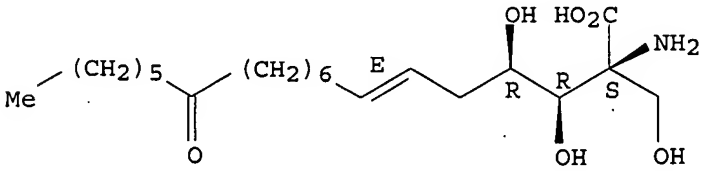
factors. However, the combination of myriocin and FB1 did not prevent FB1-increased concentration of plasma alanine aminotransferase and only slightly attenuated aspartate aminotransferase; it did not affect the FB1-induced hepatocyte apoptosis or increased cell proliferation. A longer combined treatment of myriocin and FB1 was highly toxic. The hepatotoxic effects in mice seen in this study are most likely due to a combination of factors including accumulation of free sphinganine, depletion of more complex sphingolipids and sphingomyelin, or other unknown mechanisms.

IT 35891-70-4, Myriocin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(myriocin prevented fumonisin B1-induced elevation of hepatic sphinganine and/or metabolites and cell signaling genes without ameliorating hepatotoxicity in mice)

RN 35891-70-4 CAPLUS

CN 6-Eicosenoic acid, 2-amino-3,4-dihydroxy-2-(hydroxymethyl)-14-oxo-, (2S,3R,4R,6E)- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2004:316933 CAPLUS

DN 141:186310

TI Inhibition of Serine Palmitoyltransferase by Myriocin, a Natural Mycotoxin, Causes Induction of c-myc in Mouse Liver

AU He, Quanren; Johnson, Victor J.; Osuchowski, Marcin F.; Sharma, Raghubir P.

CS College of Veterinary Medicine, Department of Physiology and Pharmacology, The University of Georgia, Athens, GA, 30602-7389, USA

SO Mycopathologia (2004), 157(3), 339-347
CODEN: MYCPAH; ISSN: 0301-486X

PB Kluwer Academic Publishers

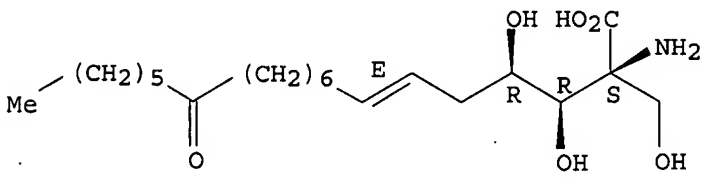
DT Journal

LA English

AB Myriocin, a fungal metabolite isolated from Myriococcum albomyces, Isaria sinclairi, and Mycelia sterilia, is a potent inhibitor of serine palmitoyltransferase (SPT), a key enzyme in de novo synthesis of sphingolipids. To evaluate the biol. effects of myriocin in vivo, the authors investigated the levels of free sphingoid bases and expression of selected genes regulating cell growth in mouse liver. Male Balb/c mice, weighing 22 g were injected i.p. with myriocin at 0, 0.1, 0.3, and 1.0 mg kg-1 body weight daily for 5 days. Animals were euthanized 24 h after the last treatment. Levels of plasma alanine aminotransferase and aspartate aminotransferase were not significantly altered by the treatment. A dose-dependent decrease in free sphinganine but not sphingosine was detected by HPLC in both liver and kidney. The decrease of free sphinganine paralleled the decrease in SPT activity. Reverse transcriptase polymerase chain reaction anal. on liver mRNA revealed an increase in expression of c-myc, but no changes in tumor necrosis factor α, transforming growth factor β, and hepatocyte growth factor. Results showed that myriocin blocked de novo synthesis of sphingolipids in vivo by SPT inhibition and induced c-myc expression in liver.

IT 35891-70-4, Myriocin
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(inhibition of serine palmitoyltransferase by myriocin, a natural mycotoxin, causes induction of c-myc in mouse liver)
RN 35891-70-4 CAPLUS
CN 6-Eicosenoic acid, 2-amino-3,4-dihydroxy-2-(hydroxymethyl)-14-oxo-, (2S,3R,4R,6E)- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s l2 and adipocyte
14913 ADIPOCYTE
L4 1 L2 AND ADIPOCYTE

=> d

L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:823310 CAPLUS
DN 143:206468
TI Ceramide de novo synthesis-based methods for modulation of mature SREBP, and related therapeutic methods and articles of manufacture
IN Worgall, Tilla S.; Deckelbaum, Richard J.
PA USA
SO U.S. Pat. Appl. Publ., 45 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005182020	A1	20050818	US 2003-712684	20031114
PRAI US 2003-712684		20031114		

=> s l2 and sterol regulatory element bindign proteins
24830 STEROL
172202 REGULATORY
749754 ELEMENT
2 BINDIGN
1395528 PROTEINS
0 STEROL REGULATORY ELEMENT BINDIGN PROTEINS
(STEROL(W)REGULATORY(W)ELEMENT(W)BINDIGN(W)PROTEINS)
L5 0 L2 AND STEROL REGULATORY ELEMENT BINDIGN PROTEINS

=> s l2 and sterol regulatory element bindign protein
24830 STEROL
172202 REGULATORY
749754 ELEMENT
2 BINDIGN
1995807 PROTEIN
0 STEROL REGULATORY ELEMENT BINDIGN PROTEIN
(STEROL(W)REGULATORY(W)ELEMENT(W)BINDIGN(W)PROTEIN)

```
L6            0 L2 AND STEROL REGULATORY ELEMENT BINDIGN PROTEIN

=> s l2 and sterol regulatory element binding protein
         24830 STEROL
        172202 REGULATORY
        749754 ELEMENT
        972455 BINDING
       1995807 PROTEIN
          1389 STEROL REGULATORY ELEMENT BINDING PROTEIN
                 (STEROL(W)REGULATORY(W)ELEMENT(W)BINDING(W)PROTEIN)
L7            2 L2 AND STEROL REGULATORY ELEMENT BINDING PROTEIN

=> d 1-2 bib abs

L7   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2007 ACS on STN
AN   2006:1140230  CAPLUS
DN   146:19933
TI   Modulation of lipoprotein metabolism by inhibition of sphingomyelin
     synthesis in ApoE knockout mice
AU   Park, Tae-Sik; Panek, Robert L.; Rekhter, Mark D.; Mueller, Sandra Bak;
     Rosebury, Wendy S.; Robertson, Andrew; Hanselman, Jeffrey C.; Kindt,
     Erick; Homan, Reynold; Karathanasis, Sotirios K.
CS   Pfizer Global Research and Development, Cardiovascular Pharmacology, Ann
     Arbor, MI, 48105, USA
SO   Atherosclerosis (Amsterdam, Netherlands) (2006), 189(2), 264-272
     CODEN: ATHSBL; ISSN: 0021-9150
PB   Elsevier B.V.
DT   Journal
LA   English
AB   Plasma sphingomyelin (SM) has been suggested as a risk factor for coronary
     heart disease independent of cholesterol levels.  A decrease of SM in
     lipoproteins is known to improve the activities of lecithin:cholesterol
     acyltransferase (LCAT) and lipoprotein lipase (LPL) in vitro.  Inhibition
     of SM biosynthesis may reduce lipoprotein SM content and thus improve
     cholesterol distribution in lipoproteins by enhancing reverse cholesterol
     transport and clearance of triglyceride-rich lipoproteins.  To examine
     this hypothesis, ApoE KO mice were fed a western diet and treated for 4 wk
     with various concns. of myriocin, a specific inhibitor of serine
     palmitoyltransferase.  Myriocin treatment lowered plasma cholesterol and
     TG levels in a dose-dependent manner.  In addition, myriocin treatment
     reduced cholesterol contents in VLDL and LDL and elevated HDL-cholesterol.
     Observed lipid-lowering effects of myriocin were associated with suppression of
     HMG CoA reductase and fatty acid synthase via reduced levels of SREBP-1
     RNA and protein.  Induction of apoAI and lecithin:cholesterol
     acytransferase (LCAT) in the liver by myriocin was associated with an
     increased HDL.  Lesion area and macrophage area were also diminished in
     the cuffed femoral artery of ApoE KO mice.  In conclusion, inhibition of
     sphingolipid biosynthesis can be a novel therapeutic target for
     dyslipidemia and atherosclerosis.
RE.CNT  35    THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7   ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2007 ACS on STN
AN   2005:823310  CAPLUS
DN   143:206468
TI   Ceramide de novo synthesis-based methods for modulation of mature SREBP,
     and related therapeutic methods and articles of manufacture
IN   Worgall, Tilla S.; Deckelbaum, Richard J.
PA   USA
SO   U.S. Pat. Appl. Publ., 45 pp.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
```

PI	US 2005182020	A1	20050818	US 2003-712684	20031114
PRAI	US 2003-712684		20031114		

AB A method is described for decreasing the amount of mature SREBP (mSREBP) in a cell characterized by an elevated level of mSREBP comprising contacting the cell with an agent that specifically inhibits de novo synthesis of ceramide in the cell, thereby decreasing the amount of mSREBP in the cell. Also described are related therapeutic methods and articles of manufacture

=> s l2 and cell
2203048 CELL
L8 35 L2 AND CELL

=> d 1-35 bib abs

L8 ANSWER 1 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2007:205640 CAPLUS
DN 146:302263
TI Intravascular stent coatings for release of antioxidants for the treatment of radical-mediated cell injury caused by the reperfusion after ischemia
IN Chen, Wenbing; Wang, Ran; Zhang, Zhigang; Liu, Bozhi
PA Tianjin Baichang Medical Instrument Technology Co., Ltd., Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 11pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	CN 1911459	A	20070214	CN 2006-10015368	20060818
PRAI	CN 2006-10015368		20060818		

AB The title intravascular stent coating comprises 1-90% of antioxidant or a combination of antioxidant and anti-restenosis agents, and 10-99% of carrier. The antioxidant can be one of superoxide dismutase, catalase, coenzyme Q10, glutathione peroxidase, lycopene, reduced glutathione, vitamin E, β-carotene, vitamin C, and trace elements such as Zn, Se, Cr, and Mn. The antioxidant and anti-restenosis agent are uniformly attached to the surface of a stent by mixing and coating or coating layer by layer. The stent coating can effectively relieve or reduce radical-mediated injuries to human cells and tissues during reperfusion after ischemia, and realize successful treatment of cardiac insufficiency.

L8 ANSWER 2 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2007:152773 CAPLUS
DN 146:352810
TI Expression, activity, and role of serine palmitoyltransferase in the rat hippocampus after kainate injury
AU He, Xin; Guan, Xue-Li; Ong, Wei-Yi; Farooqui, Akhlaq A.; Wenk, Markus R.
CS Department of Anatomy, National University of Singapore, Singapore, Singapore
SO Journal of Neuroscience Research (2007), 85(2), 423-432
CODEN: JNREDK; ISSN: 0360-4012
PB Wiley-Liss, Inc.
DT Journal
LA English
AB An increase in ceramide species was shown recently by lipid anal. of the rat hippocampus after kainate-induced excitotoxic injury. In this study, the authors showed increased expression of serine palmitoyltransferase (SPT), the 1st enzyme in the ceramide biosynthetic pathway, in reactive astrocytes of the hippocampus after kainate injections. The increase in enzyme expression was paralleled by increased SPT enzyme activity in the hippocampus at 2 wk post-kainate injection. In vitro studies showed that treatment of hippocampal slice cultures with SPT inhibitor ISP-1

(myriocin) or L-cycloserine modulated increases in 16:0, 18:0, and 20:0 ceramide species, and partially reduced kainate-induced cell death. The above findings indicate a role of SPT in ceramide increase after kainate injury, although addnl. effects of sphingomyelinase cannot be ruled out. They also suggest that SPT activity might contribute to neuronal injury after kainate excitotoxicity.
RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:372271 CAPLUS
DN 145:306151
TI In vitro evaluation of the effect of a novel immunosuppressive agent, FTY720, on the function of feline neutrophils
AU Chen, Yi-Je; Kyles, Andrew E.; Gregory, Clare R.
CS Comparative Transplantation Laboratory, Department of Surgical and Radiological Sciences and the Center for Companion Animal Health, School of Veterinary Medicine, University of California, Davis, CA, 95616-8745, USA
SO American Journal of Veterinary Research (2006), 67(4), 588-592
CODEN: AJVRAH; ISSN: 0002-9645
PB American Veterinary Medical Association
DT Journal
LA English
AB Objective:To use in vitro assays to evaluate the effects of a novel immunosuppressive agent, FTY720, on biol. functions (migration, phagocytosis, and production of reactive-oxygen species [ROS]) of feline peripheral neutrophils and determine the cytotoxic effects of FTY720 on feline peripheral neutrophils. Sample Population:Peripheral neutrophils obtained from 8 healthy cats. Procedure:Peripheral neutrophils were isolated from blood samples obtained from the 8 cats and exposed to the phosphorylated form of FTY720 (FTY720-P). A fluorescence-based in vitro evaluation of migration was performed. Phagocytosis of microbes and production of ROS were evaluated by use of a 2-color flow cytometry system. Samples of whole blood obtained from the cats were incubated with various concns. of FTY720-P, fluorescein-labeled Staphylococcus aureus, and dihydroethidium. Cytotoxic effects were evaluated by use of propidium iodide staining. Results:Addition of FTY720-P caused a slight nonsignificant decrease in phagocytosis and production of ROS by feline peripheral neutrophils. Migration activity of feline peripheral neutrophils was significantly increased by the addition of FTY720-P. Addition of FTY720-P at concns. considered for clin. use did not increase the death rate of feline peripheral neutrophils. Conclusions and Clin. Relevance:FTY720 does not inhibit critical functions of feline peripheral neutrophils in vitro.
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:1258979 CAPLUS
DN 144:324413
TI Effect of FTY720 on Chronic Cyclosporine Nephropathy in Rats
AU Kim, Jin Young; Lim, Sun Woo; Li, Can; Kim, Jung Shim; Ahn, Kyung Ohk; Yang, Hyun Joo; Choi, Bum Soon; Kim, Yong Soo; Kim, Jin; Bang, Byung Kee; Yang, Chul Woo
CS Xenotransplantation Center, Division of Internal Medicine, The Catholic University of Korea, Seoul, S. Korea
SO Transplantation (2005), 80(9), 1323-1330
CODEN: TRPLAU; ISSN: 0041-1337
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Background: Long-term treatment with cyclosporine A (CsA) causes tubulointerstitial inflammation and fibrosis in the kidney. To define the role of lymphocytes in this process, the novel lymphocyte-specific inhibitor FTY720 was administered to rats with exptl. model of chronic CsA

nephropathy. Methods: Sprague-Dawley rats were treated daily for 4 wk with CsA (7.5 mg/kg), or both CsA and FTY720 (0.125 mg/kg). The effects of FTY720 on CsA-induced renal injury were evaluated using renal function tests and histopathol., and the expression of mediators of CsA-induced renal injury (osteopontin, transforming growth factor-beta1 [TGF-β1], βig-h3, and angiotensin II). Results: FTY720 treatment significantly decreased T-lymphocyte accumulation in kidneys compared with CsA treatment alone. FTY720 treatment improved not only CsA-induced renal dysfunction but also renal histopathol., demonstrated by decreased macrophage infiltration and interstitial fibrosis. Increased osteopontin, TGF-β1, βig-h3, and angiotensin II expression in CsA-treated rat kidneys were decreased with FTY720 treatment. Conclusions: FTY720 treatment prevents CsA-induced renal injury.

RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:1075623 CAPLUS
DN 143:339656
TI Use of a serine palmitoyltransferase (spt) inhibitor to treat atherosclerosis and dyslipidemia
IN Homan, Reynold; Karathanasis, Sotirios Konstantinou; Panek, Robert Lee; Park, Tae-Sik; Rekhter, Mark David
PA Warner-Lambert Company LLC, USA
SO PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005092325	A1	20051006	WO 2005-IB733	20050321
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2560920	A1	20051006	CA 2005-2560920	20050321
	EP 1732538	A1	20061220	EP 2005-708781	20050321
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
PRAI	US 2004-557021P	P	20040326		
	WO 2005-IB733	W	20050321		

AB The invention relates to methods of treating atherosclerosis, dyslipidemia, other cardiovascular diseases and related diseases, such as diabetes, using a serine palmitoyltransferase (SPT) inhibitor. The invention also relates to pharmaceutical compns. and kits that comprise a serine palmitoyltransferase (SPT) inhibitor, optionally with another pharmaceutical agent. SPT inhibitor myriocin was shown to lower plasma cholesterol and triglycerides and decrease atherosclerotic lesions in aortas of ApoE KO mice.

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:953103 CAPLUS
DN 144:427181
TI Ethanol-Induced Changes in the Content of Triglycerides, Ceramides, and Glucosylceramides in Cultured Neurons

AU Saito, Mariko; Saito, Mitsuo; Cooper, Thomas B.; Vadasz, Csaba
CS Laboratory of Neurobehavior Genetics and the Division of Analytical Psychopharmacology, The Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, 10962, USA
SO Alcoholism: Clinical and Experimental Research (2005), 29(8), 1374-1383
CODEN: ACRSDM; ISSN: 0145-6008
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Ethanol induces apoptosis in cultured neurons. To assess the involvement of sphingolipids and neutral lipids in the apoptotic process, ethanol-induced alterations in lipid content and metabolism were examined by using primary cultured rat cerebellar granule neurons (CGNs), human neuroblastoma SK-N-SH cells, and mouse neuroblastoma Neuro2a cells. Ethanol treatment conditions that induced apoptosis in CGNs and SK-N-SH cells but not in Neuro2A cells were used for these expts. Cultured neurons were treated with and without 100 mM ethanol for 1-3 days, and the amts. of cellular sphingolipids [ceramide, glucosylceramide (GlcCer), and sphingomyelin] and neutral lipids [cholesterol, triglyceride (TG), and cholesterol ester (ChE)] were analyzed by high-performance thin-layer chromatog., using a Coomassie brilliant blue staining method. The incorporation of [C] acetate into each lipid fraction was measured in CGNs treated with and without ethanol. Also, the effect of delipidated serum, sterols, myriocin (a serine-palmitoyltransferase inhibitor), and desipramine (an acid sphingomyelinase inhibitor) on ethanol-induced lipid changes was studied by using Neuro2A cells. The most prominent change common to CGN, SK-N-SH, and Neuro2A cells was ethanol-induced TG accumulation. Higher incorporation of radioactivity into TG was also observed in ethanol-treated cultures when cellular lipids were metabolically labeled with [C] acetate in CGNs. In addition, ethanol elevated ceramide levels in all these neurons. However, ethanol induced decreases in GlcCer along with the reduction of cell viability in SK-N-SH cells and CGNs, whereas it increased GlcCer in Neuro2A cells that remained viable. Myriocin, which reduced ceramide levels, attenuated ethanol-induced cell death in SK-N-SH cells. Ethanol-induced accumulation of TG was sterol-independent, whereas changes in ceramide and GlcCer were affected in Neuro2A cells by the presence of sterols in the medium. Staurosporine, which induced cell death in SK-N-SH cells, increased levels of TG, ChE, and ceramides and reduced the level of GlcCer. The results showing that ethanol induces the accumulation of TG and ceramide in cultured neurons suggest that ethanol enhances lipogenesis and(or) reduces fatty acid degradation in neurons, as previously observed in other cell types. Further, ethanol-induced changes in lipid metabolism, specifically those of ceramide and GlcCer, may be related to the ethanol-induced apoptotic pathway.
RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:823310 CAPLUS
DN 143:206468
TI Ceramide de novo synthesis-based methods for modulation of mature SREBP, and related therapeutic methods and articles of manufacture
IN Worgall, Tilla S.; Deckelbaum, Richard J.
PA USA
SO U.S. Pat. Appl. Publ., 45 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2005182020	A1	20050818	US 2003-712684	20031114
PRAI US 2003-712684		20031114		

AB A method is described for decreasing the amount of mature SREBP (mSREBP) in

a cell characterized by an elevated level of mSREBP comprising contacting the cell with an agent that specifically inhibits de novo synthesis of ceramide in the cell, thereby decreasing the amount of mSREBP in the cell. Also described are related therapeutic methods and articles of manufacture

L8 ANSWER 8 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:379228 CAPLUS
DN 143:74620
TI Disturbance of Sphingolipid Biosynthesis Abrogates the Signaling of Mss4, Phosphatidylinositol-4-phosphate 5-Kinase, in Yeast
AU Kobayashi, Takafumi; Takematsu, Hiromu; Yamaji, Toshiyuki; Hiramoto, Shinsuke; Kozutsumi, Yasunori
CS Laboratory of Membrane Biochemistry and Biophysics, Graduate School of Biostudies, Kyoto University, Kyoto, 606-8501, Japan
SO Journal of Biological Chemistry (2005), 280(18), 18087-18094
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB The functional relationships between phosphoinositides and sphingolipids have not been well characterized to date. ISP-1/myriocin is a potent inhibitor of sphingolipid biosynthesis and induces severe growth defects in eukaryotic cells because of the sphingolipid deprivation. We characterized a novel multicopy suppressor gene of ISP-1-mediated cell death in yeast, MSS4. MSS4 encodes a phosphatidylinositol-4-phosphate 5-kinase that synthesizes phosphatidylinositol (4,5)-bisphosphate (PI4,5P2). We demonstrate here that ISP-1 treatment of yeast causes defects both in the activity and subcellular localization of Mss4. The effect of the Mss4 defect on the downstream signaling was examined, because interaction between the Mss4 product, PI4,5P2, and the pleckstrin-homol. domain of Rom2 mediates recruitment of Rom2 to the membrane, which is the crucial step for subsequent Rho1/2 activation. Indeed, failure of Rom2 recruitment was observed in ISP-1-treated cells as well as in csg2-deleted cells, which have reduced mannosylated inositolphosphorylceramide. These data suggested that proper sphingolipids are required for the signaling pathway involving Mss4.
RE.CNT 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:326221 CAPLUS
DN 142:458423
TI Myriocin prevents fumonisin B1-induced sphingoid base accumulation in mice liver without ameliorating hepatotoxicity
AU He, Quanren; Riley, Ronald T.; Sharma, Raghubir P.
CS Department of Physiology and Pharmacology, College of Veterinary Medicine, University of Georgia, Athens, GA, 30602-7389, USA
SO Food and Chemical Toxicology (2005), 43(6), 969-979
CODEN: FCTOD7; ISSN: 0278-6915
PB Elsevier B.V.
DT Journal
LA English
AB Fumonisin B1 (FB1), a mycotoxin produced by Fusarium verticillioides present on corn and corn-based products, causes species- and organ-specific diseases. The hepatotoxic effects of FB1 in mice were closely correlated with the accumulation of free sphinganine, a marker for ceramide synthase inhibition, and reduced biosynthesis of more complex sphingolipids. It was shown that FB1 modulates expression of many cell signaling factors. In the current study the authors used myriocin, a specific inhibitor of serine palmitoyltransferase, to investigate the role of free sphinganine accumulation in FB1-induced hepatotoxicity and increased expression of selected signaling genes in BALB/c mice. The mice were pretreated daily with i.p. injection of 1.0 mg/kg myriocin 30 min before s.c. injections of 2.25 mg/kg of FB1 for 3

days. Results showed that myriocin alone was not hepatotoxic and the combination of myriocin plus FB1 completely prevented the FB1-induced elevation of hepatic free sphinganine and prevented the FB1-induced induction of selected cell signaling genes, suggesting that accumulation of free sphinganine and/or its metabolites contribute to the FB1-modulation of the cell signaling factors. However, the combination of myriocin and FB1 did not prevent FB1-increased concentration of plasma alanine aminotransferase and only slightly attenuated aspartate aminotransferase; it did not affect the FB1-induced hepatocyte apoptosis or increased cell proliferation. A longer combined treatment of myriocin and FB1 was highly toxic. The hepatotoxic effects in mice seen in this study are most likely due to a combination of factors including accumulation of free sphinganine, depletion of more complex sphingolipids and sphingomyelin, or other unknown mechanisms.

RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 10 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:308652 CAPLUS
DN 143:3896
TI The requirement for the hydrophobic motif phosphorylation of Ypk1 in yeast differs depending on the downstream events, including endocytosis, cell growth, and resistance to a sphingolipid biosynthesis inhibitor, ISP-1
AU Tanoue, Daisuke; Kobayashi, Takafumi; Sun, Yidi; Fujita, Tetsuro; Takematsu, Hiromu; Kozutsumi, Yasunori
CS Laboratory of Membrane Biochemistry and Biophysics, Graduate School of Biostudies, Kyoto University, Kyoto, 606-8501, Japan
SO Archives of Biochemistry and Biophysics (2005), 437(1), 29-41
CODEN: ABBIA4; ISSN: 0003-9861
PB Elsevier
DT Journal
LA English
AB ISP-1 inhibits de novo sphingolipid biosynthesis and induces growth defects in both mammals and yeast (Saccharomyces cerevisiae). In our previous study, YPK1/SLI2 was identified as one of multicopy suppressor genes for ISP-1 in yeast. Ypk1 is proposed to be a downstream serine/threonine kinase of the sphingolipid signaling pathway in yeast. Other than resistance against ISP-1, Ypk1 is involved in at least two downstream events, namely cell growth and endocytosis. In this study, the effect of mutants of Ypk1 on these three downstream events was investigated. Among Ypk1 mutants, no kinase-dead' mutants complemented the defects in any of these three downstream events in the ypk1 null strain. One of the hydrophobic motif phosphorylation-deficient mutants of Ypk1, Ypk1T662A had the moderate kinase activity compared with the wild-type Ypk1. Ypk1T662A and the wild-type Ypk1 completely restored the slow-growth phenotype and fluid-phase endocytosis defect of the ypk1 null strain. However, unlike the wild-type Ypk1, Ypk1T662A lost the ability for the recovery of the ISP-1 resistance in the ypk1 null strain. Furthermore, the expression of Ypk1T662A in the wild-type strain showed a dominant-neg. effect on the ISP-1-resistance activity. On the other hand, the cell growth revertant of the ypk1 null strain still showed the hypersensitive phenotype to ISP-1. These data suggest that the ISP-1-resistance pathway is under the regulation of the hydrophobic motif phosphorylation and is separated from the other pathways downstream of Ypk1.

RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 11 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:223797 CAPLUS
DN 142:385619
TI Effect of Myriocin on Plasma Sphingolipid Metabolism and Atherosclerosis in apoE-deficient Mice
AU Hojjati, Mohammad Reza; Li, Zhiqiang; Zhou, Hongwen; Tang, Songshan; Huan, Chongmin; Ooi, Everlyn; Lu, Shendi; Jiang, Xian-Cheng

CS Department of Anatomy and Cell Biology, State University of New York Downstate Medical Center, Brooklyn, NY, 11203, USA
SO Journal of Biological Chemistry (2005), 280(11), 10284-10289
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB Sphingolipids play a very important role in cell membrane formation, signal transduction, and plasma lipoprotein metabolism, all of which may well have an impact on the development of atherosclerosis. To investigate the relationship between sphingolipid metabolism and atherosclerosis, we utilized myriocin to inhibit mouse serine palmitoyl-CoA transferase (SPT), the key enzyme for sphingolipid biosynthesis. We injected 8-wk-old apoE-deficient mice with myriocin (0.3 mg/kg/every other day, i.p.) for 60 days. On a chow diet, myriocin treatment caused a significant decrease (50%) in liver SPT activity ($p < 0.001$), significant decreases in plasma sphingomyelin, ceramide, and sphingosine-1-phosphate levels (54, 32, and 73%, resp.) ($p < 0.0001$), and a significant increase in plasma phosphatidylcholine levels (91%) ($p < 0.0001$). Plasma total cholesterol and triglyceride levels demonstrated no significant changes, but there was a significant decrease in atherosclerotic lesion area (42% in root and 36% in en face assays) ($p < 0.01$). On a high fat diet, myriocin treatment caused marked decreases in plasma sphingomyelin, ceramide, and sphingosine-1-phosphate levels (59, 66, and 81%, resp.) ($p < 0.0001$), and a marked increase in plasma phosphatidylcholine levels (100%) ($p < 0.0001$). Total cholesterol and triglyceride demonstrated no significant changes, but there was a significant decrease in atherosclerotic lesion area (39% in root and 37% in en face assays) ($p < 0.01$). These results indicate that, apart from cholesterol levels, sphingolipids have an effect on atherosclerotic development and that SPT has proatherogenic properties. Thus, inhibition of SPT activity could be an alternative treatment for atherosclerosis.
RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 12 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:1057420 CAPLUS
DN 142:193189
TI Fungal Metabolite Sulfamisterin Suppresses Sphingolipid Synthesis through Inhibition of Serine Palmitoyltransferase
AU Yamaji-Hasegawa, Akiko; Takahashi, Atsushi; Tetsuka, Yasuyuki; Senoh,. Yukiko; Kobayashi, Toshihide
CS RIKEN, Wako, Saitama, 351-0198, Japan
SO Biochemistry (2005), 44(1), 268-277
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
OS CASREACT 142:193189
AB Sphingolipids and their metabolites are known to modulate various cellular events including proliferation, differentiation, and apoptosis. Serine palmitoyltransferase (SPT) is the enzyme that catalyzes the first step of the biosynthesis of all sphingolipids. Here, we report that a newly identified antibiotic, sulfamisterin, derived from the fungus Pycnidiella sp., is a specific inhibitor of SPT. The chemical structure of sulfamisterin resembles both that of sphingosine as well as a potent inhibitor of SPT, ISP-1 (myriocin). Sulfamisterin inhibited SPT activity with IC50 = 3 nM in a cell-free lysate prepared from Chinese hamster ovary (CHO) fibroblasts. Sulfamisterin markedly inhibited the biosynthesis of sphingolipids in living CHO cells and in yeast Saccharomyces cerevisiae as monitored by radioactive precursors. Unlike the cell-free expts., 10 μM sulfamisterin was required for complete inhibition of sphingolipid biosynthesis in intact cells. We also synthesized a series of structural analogs of sulfamisterin and examined their activities both in cell-free and in living cell systems.

RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 13 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:1045478 CAPLUS
DN 142:417243
TI Multi-coat medicine-delivering scaffold
IN Zhang, Yi; Tang, Zhirong; Gao, Runlin
PA Weichuang Medical Instruments Shanghai Co., Ltd., Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 13 pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	CN 1465410	A	20040107	CN 2002-146905	20021024
	WO 2004002367	A1	20040108	WO 2003-CN489	20030625
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2003280437	A1	20040119	AU 2003-280437	20030625
	JP 2005531391	T	20051020	JP 2004-548875	20030625
PRAI	CN 2002-112242	A	20020627		
	CN 2002-146905	A	20021024		
	CN 2002-155138	A	20021217		
	CN 2003-115596	A	20030228		
	CN 2003-116063	A	20030328		
	CN 2003-128906	A	20030528		
	WO 2003-CN489	W	20030625		

AB The multi-coat medicine-delivering scaffold consists of a scaffold, a bottom layer, ≥2 medicine-loading layers, and a surface layer. The medicine-loading layer is composed of active component 0.5-99, polymer 0.5-99, and additive 0-10%. The surface layer is composed of active component 0-99, polymer 0.5-99, and additive 0-10%. The medicine is anti-thrombogenic agent, antitumor agent, immunosuppressant, hormone, anti-restenosis agent, or carrier-loaded gene. The anti-thrombogenic agent is heparin, aspirin, hirudin, colchicine, etc. The antitumor agent is methotrexate, epothilones, antibiotic, hormone, antibody, etc. The immunosuppressant is cyclosporin A, FK506, 15-deoxyspergualin, MMF, rapamycin or its derivative, FE900,520, FR900,523, NK86-1,086, daclizumab, etc. The anti-restenosis agent is batimastat, 17beta-estradiol, 2-chlorodeoxyadenosine, 2-deoxycoformycin, etc. The gene loaded by cell, virus, plasmid, polymer, etc is keratin 8 gene, vascular endothelia growth factor gene, epidermal growth factor gene, etc. The scaffold is processed from polylactic acid, polyglycolic acid, poly-epsilon-caprolactone, celluloses, polyvinylpyrrolidone, polyvinyl alc., gelatin, Na alginate, ethylene-vinyl acetate copolymer, poly(Me methacrylate), etc. The additive is crosslinking curing agent, wetting dispersing agent, and plasticizer. The multi-coat medicine-delivering scaffold may be used in intervention therapy for cardiovascular blocking, nerve blocking, and peripheral vessel blocking.

L8 ANSWER 14 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:947989 CAPLUS
DN 142:232571
TI Fenretinide stimulates redox-sensitive ceramide production in breast cancer cells: potential role in drug-induced cytotoxicity

AU Rehman, F.; Shanmugasundaram, P.; Schrey, M. P.
CS Imperial College London, Section of Endocrinology & Metabolic Medicine, St Mary's Hospital, London, W2 1NY, UK
SO British Journal of Cancer (2004), 91(10), 1821-1828
CODEN: BJCAAI; ISSN: 0007-0920
PB Nature Publishing Group
DT Journal
LA English
AB The synthetic retinoid N-(4-hydroxphenyl) retinamide (4HPR) has manifold actions, which may contribute to its chemopreventive effects on breast cancer cell growth and progression. A role for ceramide as a stress-response signal is investigated here during the cytotoxic action of 4HPR in MCF-7 cells. N-(4-hydroxphenyl) retinamide induced a dose-dependent decline in cell growth and survival associated with a maximal 10-fold increase in ceramide production at 10 μM. N-(4-hydroxphenyl) retinamide exhibited a greater potency than all-trans retinoic acid (ATRA) on growth inhibition and ceramide production The synthetic peroxisome proliferator-activated receptors agonist troglitazone (TGZ), but not the native ligand 15-deoxy-delta 12,14-prostaglandin J2, abrogated both these actions of 4HPR but not that of ATRA. The antioxidant N-acetylcysteine mimicked the abrogative effect of TGZ on 4HPR action, while the exogenous oxidant H2O2 also stimulated ceramide production The inhibitors of de novo ceramide synthesis, fumonisin B1 and myriocin, blocked the ceramide response to 4HPR and partially reversed the apoptotic response, but did not prevent the overall decline in cell survival. The pancaspase inhibitor Z-VAD fmk reduced the decrease in cell survival caused by 4HPR, but did not affect the ceramide response. These findings describe a novel redox-sensitive elevation of ceramide levels associated with the cytotoxic response of breast cancer cells to 4HPR. However, a major mediatory role for this sphingolipid in this context remains equivocal.
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 15 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:875226 CAPLUS
DN 142:50573
TI Altered de novo sphingolipid biosynthesis is involved in the serum deprivation-induced cell death in LLC-PK1 cells
AU Yu, Min; Yoo, Jae; Lee, Youn; Lee, Yong; Hong, Jin; Oh, Ki; Song, Sukgil; Yun, Yeo; Yoo, Hwan; Oh, Sei
CS College of Pharmacy, Chungbuk National University, Cheongju, S. Korea
SO Journal of Toxicology and Environmental Health, Part A (2004), 67(23-24), 2085-2094
CODEN: JTEHF8; ISSN: 1528-7394
PB Taylor & Francis, Inc.
DT Journal
LA English
AB Fumonisin B1, a specific inhibitor of ceramide synthase, and ISPI (Myriocin), a serine palmitoyltransferase inhibitor, modulate the de novo sphingolipid biosynthesis pathway. This study was conducted to determine whether serum deprivation-induced cell death is regulated by de novo sphingolipid biosynthesis in pig kidney LLC-PK1 cells. Serum withdrawal from the culture medium produced cell death in LLC-PK1 cells. Fumonisin B1 at concns. ranging from 5μM to 30μM delayed until 48 h this cell death resulting from the absence of fetal bovine serum (FBS) in cell culture. Pretreatment of cultured cells with fumonisin B1 in the presence of serum for 24 h increased by approx. 70% this cytoprotective activity of fumonisin B1 against serum deprivation-induced cell death. Serum deprivation increased sphingolipid biosynthesis threefold compared to 5% serum-enriched culture. Fumonisin B1 at 5-30 μM lowered the content of total complex sphingolipids to levels of 50% and 77% of the content in serum-enriched culture, although the concentration of intracellular free sphinganine was elevated. ISPI alone at greater than 1 nMconcn. reduced

total complex sphingolipid content to values in LLC-PK1 cells grown in the presence of 5% FBS. The results suggest that the de novo complex sphingolipid biosynthesis modulated by either fumonisin B1 or ISPI may regulate serum deprivation-induced cell death in LLC-PK1 cells.
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 16 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:645031 CAPLUS
DN 141:326980
TI Disruption of sphingolipid homeostasis by myriocin, a mycotoxin, reduces thymic and splenic T-lymphocyte populations
AU Johnson, Victor J.; He, Quanren; Osuchowski, Marcin F.; Sharma, Raghubir P.
CS College of Veterinary Medicine, Department of Physiology and Pharmacology, The University of Georgia, Athens, GA, 30602-7389, USA
SO Toxicology (2004), 201(1-3), 67-75
CODEN: TXCYAC; ISSN: 0300-483X
PB Elsevier Ireland Ltd.
DT Journal
LA English
AB Myriocin is a naturally occurring fungal metabolite possessing potent immunosuppressive properties. The biochem. mechanism of action of this compound is inhibition of serine palmitoyltransferase (SPT), the key rate limiting enzyme in sphingolipid biosynthesis, intermediates of which are important mediators of immune signaling. Previous studies have shown that myriocin strongly suppressed immune function with T-lymphocyte functions being most sensitive. To further our understanding of the mechanisms of this effect, we investigated the impact of subacute treatment with myriocin on lymphocyte populations in the thymus and spleen of male BALB/c mice following i.p. injection of myriocin at 0, 0.1, 0.3, and 1.0 mg/kg daily for 5 consecutive days. Cellular anal. of the thymus demonstrated that total cellularity was dose-dependently reduced and the reduction was significant in mice treated with 1.0 mg/kg myriocin. Phenotyping showed that CD4+ and CD4+/CD8+ double pos. lymphocyte populations were sensitive to myriocin. No change in total cellularity of the spleen was noted but there was a significant reduction in the CD4+ lymphocyte population in mice treated with 1.0 mg/kg myriocin. There was a strong pos. correlation between total CD4+ lymphocytes in the thymus and those in the spleen. Anal. of sphingolipid levels showed a dose-dependent reduction of sphinganine in the thymus, which were pos. correlated with all redns. in lymphocyte populations. These results suggest that the immunosuppressive properties of myriocin may be due to diminished T-lymphocyte populations likely related to inhibition of SPT and disruption of sphingolipid homeostasis.
RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 17 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:436444 CAPLUS
DN 141:388255
TI Resveratrol structure and ceramide-associated growth inhibition in prostate cancer cells
AU Sala, G.; Minutolo, F.; Macchia, M.; Sacchi, N.; Ghidoni, R.
CS Laboratory of Biochemistry and Molecular Biology, San Paolo University Hospital, School of Medicine, University of Milan, Italy
SO Drugs under Experimental and Clinical Research (2003), 29(5/6), 263-269
CODEN: DECRDP; ISSN: 0378-6501
PB Bioscience Ediprint Inc.
DT Journal
LA English
AB Resveratrol (3,4',5-trans-trihydroxystilbene) is a dietary polyphenol with chemopreventive properties present in grapes, red wine, peanuts and other edible products. The antiproliferative and proapoptotic effect of resveratrol in breast cancer cells can be traced to the accumulation of ceramide. In this study we demonstrate that resveratrol can also exert

antiproliferative/proapoptotic effects in association with the accumulation of endogenous ceramide in the androgen receptor (AR)-neg. prostate cancer cell line, PC3. Notably, resveratrol shares with other ceramide-inducing agents a phenolic moiety on its structure. For this reason we hypothesize that the phenolic moiety is critical for the ceramide-associated growth-inhibitory effects of resveratrol. We compared the ability to induce both ceramide increase and growth inhibition in PC3 cells of resveratrol and three resveratrol analogs: piceatannol (3,3',4',5-trans-tetrahydroxystilbene), with an addnl. hydroxyl group in the 3' position; trans-stilbene, the nonhydroxylated analog; and the semisynthetic 3,4',5-trimethoxy-trans-stilbene (TmS), with methoxyl groups in lieu of the hydroxyl groups. Of the three stilbenoids, only piceatannol (and not stilbene or TmS) produced ceramide-associated growth inhibition. These data point to the phenolic moiety of stilbenoids as a critical structural feature necessary to induce ceramide-associated growth inhibition.

RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 18 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:316933 CAPLUS
DN 141:186310
TI Inhibition of Serine Palmitoyltransferase by Myriocin, a Natural Mycotoxin, Causes Induction of c-myc in Mouse Liver
AU He, Quanren; Johnson, Victor J.; Osuchowski, Marcin F.; Sharma, Raghubir P.
CS College of Veterinary Medicine, Department of Physiology and Pharmacology, The University of Georgia, Athens, GA, 30602-7389, USA
SO Mycopathologia (2004), 157(3), 339-347
CODEN: MYCPAH; ISSN: 0301-486X
PB Kluwer Academic Publishers
DT Journal
LA English
AB Myriocin, a fungal metabolite isolated from Myriococcum albomyces, Isaria sinclairi, and Mycelia sterilia, is a potent inhibitor of serine palmitoyltransferase (SPT), a key enzyme in de novo synthesis of sphingolipids. To evaluate the biol. effects of myriocin in vivo, the authors investigated the levels of free sphingoid bases and expression of selected genes regulating cell growth in mouse liver. Male Balb/c mice, weighing 22 g were injected i.p. with myriocin at 0, 0.1, 0.3, and 1.0 mg kg-1 body weight daily for 5 days. Animals were euthanized 24 h after the last treatment. Levels of plasma alanine aminotransferase and aspartate aminotransferase were not significantly altered by the treatment. A dose-dependent decrease in free sphinganine but not sphingosine was detected by HPLC in both liver and kidney. The decrease of free sphinganine paralleled the decrease in SPT activity. Reverse transcriptase polymerase chain reaction anal. on liver mRNA revealed an increase in expression of c-myc, but no changes in tumor necrosis factor α, transforming growth factor β, and hepatocyte growth factor. Results showed that myriocin blocked de novo synthesis of sphingolipids in vivo by SPT inhibition and induced c-myc expression in liver.

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 19 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:96714 CAPLUS
DN 140:335552
TI Deletion of OSH3 gene confers resistance against ISP-1 in Saccharomyces cerevisiae
AU Yano, Tatsuya; Inukai, Masatoshi; Isono, Fujio
CS Lead Discovery Research Laboratories, SANKYO CO., LTD., Shinagawa-Ku, Tokyo, 2-58, Japan
SO Biochemical and Biophysical Research Communications (2004), 315(1), 228-234
CODEN: BBRCA9; ISSN: 0006-291X

PB Elsevier Science
DT Journal
LA English
AB Sphingolipids have been reported to regulate the growth and death of mammalian and yeast cells, but their precise mechanisms are unknown. In this paper, it is shown that the deletion of the oxysterol binding protein homolog 3 (OSH3) gene confers hyper resistance against ISP-1, an inhibitor of sphingolipid biosynthesis, in the yeast S. cerevisiae. Furthermore, the overexpression of the ROK1 gene, which directly binds to Osh3p, conferred resistance against ISP-1, and the deletion of the KEM1 gene, which regulates microtubule functions, exhibited ISP-1 hypersensitivity. And yet, an ISP-1 treatment caused an abnormal mitotic spindle formation, and the ISP-1-induced cell cycle arrest was rescued by the deletion of the OSH3 gene. Taken together, it is suggested that the expression levels of the OSH3 gene influence the ISP-1 sensitivity of S. cerevisiae, and the sphingolipids are necessary for normal mitotic spindle formation in which the Osh3p may play a pivotal role.
RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 20 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:8149 CAPLUS
DN 140:212838
TI Reactions of Serine Palmitoyltransferase with Serine and Molecular Mechanisms of the Actions of Serine Derivatives as Inhibitors
AU Ikushiro, Hiroko; Hayashi, Hideyuki; Kagamiyama, Hiroyuki
CS Department of Biochemistry, Osaka Medical College, Takatsuki, Osaka, 569-8686, Japan
SO Biochemistry (2004), 43(4), 1082-1092
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
AB Serine palmitoyltransferase (SPT) is a key enzyme in sphingolipid biosynthesis and catalyzes the decarboxylative condensation of L-serine and palmitoyl-CoA to 3-ketodihydrosphingosine. The authors have succeeded in the overprodn. of a water-soluble homodimeric SPT from Sphingomonas paucimobilis EY2395T in Escherichia coli. The recombinant SPT showed the characteristic absorption and CD spectra derived from its coenzyme pyridoxal 5'-phosphate. On the basis of the spectral changes of SPT, the authors have analyzed the reactions of SPT with compds. related to L-serine and product, and showed the following new aspects: First, the authors analyzed the binding of L-serine and 3-hydroxypropionate and found that the spectral change in SPT by the substrate is caused by the formation of an external aldimine intermediate and not by the formation of the Michaelis complex. Second, various serine analogs were also examined; the data indicated that the α-carboxyl group of L-serine was quite important for substrate recognition by SPT. Third, the authors focused on a series of SPT inhibitors, which have been used as convenient tools to study the cell responses caused by sphingolipid depletion. The interaction of SPT with myriocin suggested that such product-related compds. would strongly and competitively inhibit enzyme activity by forming an external aldimine in the active site of the enzyme. β-Chloro-L-alanine and L-cycloserine were found to generate characteristic PLP-adducts that produced inactivation of SPT in an irreversible manner. The detailed mechanisms for the SPT inactivation were discussed. This is the first anal. of the inhibition mechanisms of SPT by these compds., which will provide an enzymol. basis for the interpretation of the results from cell biol. expts.
RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 21 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:848290 CAPLUS
DN 140:138915

TI Involvement of endogenous ceramide in the inhibition of telomerase activity and induction of morphologic differentiation in response to all-trans-retinoic acid in human neuroblastoma cells
AU Kraveka, Jacqueline M.; Li, Li; Bielawski, Jacek; Obeid, Lina M.; Ogretmen, Besim
CS Department of Pediatrics, Division of Hematology/Oncology, Medical University of South Carolina, Charleston, SC, 29425, USA
SO Archives of Biochemistry and Biophysics (2003), 419(2), 110-119
CODEN: ABBIA4; ISSN: 0003-9861
PB Elsevier Science
DT Journal
LA English
AB In this study, we examined the role of endogenous ceramide in the inhibition of telomerase and induction of morphol. differentiation in response to all-trans-retinoic acid (ATRA) in the SK-N-SH and SK-N-AS human neuroblastoma cell lines. The results showed that ATRA inhibited the activity of telomerase significantly in a time- and dose-dependent manner, as determined by telomere repeat amplification protocol (TRAP). The inhibition of telomerase by ATRA was maximum (about 50-80% of untreated controls) at 5-10 μM for 4-8 days. Treatment of cells with ATRA (5 μM) also resulted in the inhibition of growth by about 30-70% after 4 and 8 days of treatment, resp., which was measured by trypan blue exclusion method. Measurement of accumulation of endogenous ceramide by high pressure liquid chromatog. coupled with mass spectroscopy (LC/MS) showed that treatment of cells with ATRA resulted in increased levels of mainly C24:0 and C24:1 ceramides at days 2, 4, and 8, resp. Also, treatment of cells with ATRA in the presence of myriocin blocked the accumulation of ceramide significantly, and more importantly, presence of myriocin partially prevented the inhibition of telomerase. Mechanistically, inhibition of telomerase by endogenous ceramide in response to ATRA treatment involves, at least in part, down-regulation of the expression of telomerase reverse transcriptase (hTERT) mRNA, as determined by semi-quant. RT-PCR, in these cells. In addition, the modulation of telomerase activity by ATRA correlated with the induction of morphol. differentiation, which was also blocked by myriocin, as determined by extension of neurites using phase-contrast microscopy. These results, therefore, reveal an important effect of ATRA on telomerase inhibition and induction of morphol. differentiation in human neuroblastoma cells. These data also demonstrate that endogenous ceramide is one of the upstream regulators of telomerase activity in human neuroblastoma cells in response to ATRA.
RE.CNT 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 22 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:972055 CAPLUS
DN 139:16919
TI Linking Chinese medicine and G-protein-coupled receptors
AU Im, Dong-Soon
CS College of Pharmacy, Laboratory of Pharmacology, Pusan National University, Pusan, 609-735, S. Korea
SO Trends in Pharmacological Sciences (2003), 24(1), 2-4
CODEN: TPHSDY; ISSN: 0165-6147
PB Elsevier Science Ltd.
DT Journal; General Review
LA English
AB A review. Following the purification of the immunosuppressant ISP-1 from a Chinese medicine, Japanese scientists have developed a more potent immune modulator, FTY720, that induces T-cell homing. FTY720, a promising immunosuppressant for use in patients with tissue transplants and autoimmune diseases, is currently in clin. trials. Two recent studies have elucidated that the mechanism of action of FTY720 is via a subset of G-protein-coupled receptors for the lysophospholipid mediator sphingosine-1-phosphate.
RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 23 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:952726 CAPLUS
DN 138:395628
TI Ceramide Signaling in Fenretinide-Induced Endothelial Cell Apoptosis
AU Erdreich-Epstein, Anat; Tran, Linda B.; Bowman, Nina N.; Wang, Hongtao; Cabot, Myles C.; Durden, Donald L.; Vlckova, Jitka; Reynolds, C. Patrick; Stins, Monique F.; Groshen, Susan; Millard, Melissa
CS Keck School of Medicine, Department of Pediatrics, Childrens Hospital Los Angeles, Division of Hematology-Oncology, University of Southern California, Los Angeles, CA, 90027, USA
SO Journal of Biological Chemistry (2002), 277(51), 49531-49537
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB Stress stimuli can mediate apoptosis by generation of the lipid second messenger, ceramide. Herein we investigate the mol. mechanism of ceramide signaling in endothelial apoptosis induced by fenretinide (N-(4-hydroxyphenyl)retinamide (4-HPR)). 4-HPR, a synthetic derivative of retinoic acid that induces ceramide in tumor cell lines, has been shown to have antiangiogenic effects, but the mol. mechanism of these is largely unknown. We report that 4-HPR was cytotoxic to endothelial cells (50% cytotoxicity at 2.4 μM, 90% at 5.36 μM) and induced a caspase-dependent endothelial apoptosis. 4-HPR (5 μM) increased ceramide levels in endothelial cells 5.3-fold, and the increase in ceramide was required to achieve the apoptotic effect of 4-HPR. The 4-HPR-induced increase in ceramide was suppressed by inhibitors of ceramide synthesis, fumonisin B1, myriocin, and L-cycloserine, and 4-HPR transiently activated serine palmitoyltransferase, demonstrating that 4-HPR induced de novo ceramide synthesis. Sphingomyelin levels were not altered by 4-HPR, and desipramine had no effect on ceramide level, suggesting that sphingomyelinase did not contribute to the 4-HPR-induced ceramide increase. Finally, the pancaspase inhibitor, t-butyloxycarbonyl-aspartyl[O-methyl]-fluoromethyl ketone, suppressed 4-HPR-mediated apoptosis but not ceramide accumulation, suggesting that ceramide is upstream of caspases. Our results provide the first evidence that increased ceramide biosynthesis is required for 4-HPR-induced endothelial apoptosis and present a mol. mechanism for its antiangiogenic effects.
RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 24 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:390534 CAPLUS
DN 136:381627
TI Pharmacological antagonism of fumonisin B1 cytotoxicity in porcine renal epithelial cells (LLC-PK1): A model for reducing fumonisin-induced nephrotoxicity in vivo
AU He, Quanren; Riley, Ronald T.; Sharma, Raghubir P.
CS Department of Physiology and Pharmacology, College of Veterinary Medicine, The University of Georgia, Athens, GA, 30602, USA
SO Pharmacology & Toxicology (Oxford, United Kingdom) (2002), 90(5), 268-277
CODEN: PHTOEH; ISSN: 0901-9928
PB Blackwell Publishers Ltd.
DT Journal
LA English
AB Fumonisin B1 is a mycotoxin commonly found on corn. It is hepatotoxic and nephrotoxic in domestic and exptl. animals, and causes equine leukoencephalomalacia and porcine pulmonary edema. It is a potent inhibitor of ceramide synthase. Inhibition leads to accumulation of free sphingoid bases in cells and tissues. In pig kidney epithelial cells (LLC-PK1), fumonisin B1 induces increased tumor necrosis factor α (TNFα) expression independent of the accumulation of sphingoid

bases. The objective of this study was to investigate pharmacol. approaches for intervening in fumonisin B1 toxicity using the LLC-PK1 cell model. The toxicity of fumonisin B1 was assayed using cell viability and lactate dehydrogenase (lactate dehydrogenase) release. Pretreatment of cells with myriocin, preventing sphinganine accumulates, prevented the fumonisin B1-induced decrease in cell viability and increased lactate dehydrogenase release. Modulation of adenosine receptor activity did not reduce the fumonisin B1 cytotoxicity. As with myriocin, silymarin pretreatment prevented the fumonisin B1-induced effects on cell viability and lactate dehydrogenase release. When added 6 or 24 h after treatment of cells with fumonisin B1, both myriocin and silymarin reversed the decreased cell viability and suppressed the increased lactate dehydrogenase release. Myriocin, but not silymarin, blocked the accumulation of sphinganine in fumonisin B1-treated cells. Silymarin, unlike myriocin, induced expression of TNFα to an extent similar to fumonisin B1, but pretreatment with silymarin decreased the fumonisin B1-induced TNFα expression in LLC-PK1 cells. Results suggest that the mechanisms by which myriocin and silymarin protect renal cells are different, and silymarin potentially prevents fumonisin B1-induced toxicity by modulating TNFα expression or signals downstream of the inhibition of ceramide synthase.

RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 25 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2001:798090 CAPLUS
DN 135:341174
TI Detection and treatment of atherosclerosis based on plasma sphingomyelin concentration
IN Tall, Alan R.; Jiang, Xian-Cheng
PA Trustees of Columbia University in the City of New York, USA
SO PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001080903	A1	20011101	WO 2001-US12706	20010419
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRAI US 2000-551947 A 20000419
OS MARPAT 135:341174
AB The invention concerns new enzymic methods of plasma and tissue sphingomyelin concentration measurement. Also disclosed is that human plasma sphingomyelin levels are strongly pos. correlated with atherosclerosis and coronary heart disease. Thus, the use of a quick and effective plasma sphingomyelin measurement such as the subject invention, is valuable for screening assays in vitro, in cell culture or in animals to develop drugs or other treatments aimed to lower plasma sphingomyelin levels. The findings indicate that therapies aimed at reducing plasma or tissue SM levels are likely to have therapeutic benefit. These would include inhibition of sphingomyelin synthesis in the liver or arterial wall, as well as methods to enhance clearance of sphingomyelin from plasma. Thus, compds. which inhibit sphingomyelin biosynthesis or induce sphingomyelin clearance are also disclosed.

L8 ANSWER 26 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2001:374418 CAPLUS
DN 135:165968
TI Apoptosis of CTLL-2 cells induced by an immunosuppressant, ISP-I, is caspase-3-like protease-independent
AU Yamaji, Toshiyuki; Nakamura, Sachiko; Takematsu, Hiromu; Kawasaki, Toshisuke; Kozutsumi, Yasunori
CS Department of Biological Chemistry, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, 606-8501, Japan
SO Journal of Biochemistry (Tokyo, Japan) (2001), 129(4), 521-527
CODEN: JOBIAO; ISSN: 0021-924X
PB Japanese Biochemical Society
DT Journal
LA English
AB In our previous study, the sphingosine-like immunosuppressant ISP-I was shown to induce apoptosis in the mouse cytotoxic T cell line CTLL-2. In this study, we characterized the ISP-I-induced apoptotic pathway. Although caspase-3-like protease activity increases concomitantly with ISP-I-induced apoptosis in CTLL-2 cells, the apoptosis is not inhibited by caspase-3-like protease inhibitors, i.e. DEVD-cho and z-DEVD-fmk. In contrast, sphingosine-induced apoptosis in CTLL-2 cells is caspase-3-like protease-dependent. A caspase inhibitor with broad specificity, z-VAD-fmk, protects cells from apoptosis induced by ISP-I, indicating that ISP-I-induced apoptosis is dependent on caspase(s) other than caspase-3. Overexpression of Bcl-2 or Bcl-xL suppresses the apoptosis induced by ISP-I, although sphingosine-induced apoptosis is not efficiently inhibited by Bcl-2. Finally, ISP-I-induced mitochondrial depolarization, which is thought to be a checkpoint dividing the apoptotic pathway into upstream and downstream stages, is not inhibited by DEVD-cho, but is inhibited by z-VAD-fmk. These data suggest that a pathway dependent on caspase(s) other than caspase-3 is involved upstream of mitochondrial depolarization in ISP-I-induced apoptosis.
RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 27 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2000:200993 CAPLUS
DN 133:37853
TI Specificity of inhibitors of serine palmitoyltransferase (SPT), a key enzyme in sphingolipid biosynthesis, in intact cells. A novel evaluation system using an SPT-defective mammalian cell mutant
AU Hanada, K.; Nishijima, M.; Fujita, T.; Kobayashi, S.
CS Department of Biochemistry and Cell Biology, National Institute of Infectious Diseases, Tokyo, Japan
SO Biochemical Pharmacology (2000), 59(10), 1211-1216
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier Science Inc.
DT Journal
LA English
AB In the present study, we demonstrate a model cell system for evaluating the specificity of inhibitors of serine palmitoyltransferase (SPT), the enzyme that catalyzes the first step of sphingolipid biosynthesis. The LY-B strain is a Chinese hamster ovary (CHO) cell mutant defective in SPT, and the LY-B/cLCB1 strain is a genetically corrected revertant of the mutant. Although LY-B cells grew only slightly in sphingolipid-deficient medium, their growth was restored to the level of LY-B/cLCB1 cells under sphingosine-supplied conditions, indicating that, in CHO cells, the growth inhibition caused by SPT inactivation was rescued almost fully by the metabolic complementation of sphingolipids. Cultivation of LY-B/cLCB1 cells in sphingolipid-deficient medium in the presence of 10 μM sphingofungin B and ISP-1 (myriocin, thermozymocidin), potent inhibitors of SPT activity, caused severe growth inhibition with .apprx.95% inhibition of de novo sphingolipid synthesis. The growth inhibition by sphingofungin B and ISP-1 was rescued substantially by exogenous sphingosine, whereas the cytotoxicity of two

other types of SPT inhibitor, L-cycloserine and β-chloro-L-alanine, was hardly rescued. Similar cytotoxic patterns of these inhibitors also were observed on the growth of SPT-defective LY-B cells cultured under sphingosine-supplied conditions. The SPT inhibitors did not affect metabolic conversion of exogenous [3H]sphingosine to complex sphingolipids. Thus, the cytotoxicity of sphingofungin B and ISP-1, but not L-cycloserine or β-chloro-L-alanine, is due largely to inhibition of sphingolipid synthesis by inhibiting the SPT activity.
RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 28 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1999:327910 CAPLUS
DN 131:154910
TI The identification of myriocin-binding proteins
AU Chen, James K.; Lane, William S.; Schreiber, Stuart L.
CS Howard Hughes Medical Institute, Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA, 02138, USA
SO Chemistry & Biology (1999), 6(4), 221-235
CODEN: CBOLE2; ISSN: 1074-5521
PB Current Biology Publications
DT Journal
LA English
AB Myriocin is a natural product that potently induces apoptosis of a murine cytotoxic T lymphocyte cell line (CTLL-2) and inhibits a serine palmitoyltransferase (SPT) activity that has been detected in cell exts. and is thought to initiate sphingolipid biosynthesis. Because SPT has never been biochem. purified and a comprehensive appraisal of myriocin-binding proteins has not been conducted, we isolated specific targets using myriocin-based affinity chromatog. Myriocin derivs. were synthesized and evaluated using CTLL-2 proliferation and SPT activity assays. Guided by these results, affinity chromatog. matrixes were prepared and two specific myriocin-binding proteins were isolated from CTLL-2 lysates. Analyses of these polypeptides establish conclusively that they are murine LCB1 and LCB2, mammalian homologs of two yeast proteins that have been genetically linked to sphingolipid biosynthesis. The ability of myriocin-containing matrixes to bind factors that have SPT activity and the exclusive isolation of LCB1 and LCB2 as myriocin-binding proteins demonstrates that the two proteins are directly responsible for SPT activity and that myriocin acts directly upon these polypeptides.
RE.CNT 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 29 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1998:774604 CAPLUS
DN 130:20123
TI Action mechanism of immunosuppressant, ISP-1
AU Yamaji, Toshiyuki; Sun, Yidi; Kozutsumi, Yasunori
CS Grad. Sch. Pharm. Sci., Kyoto Univ., Kyoto, 606-8501, Japan
SO Tanpakushitsu Kakusan Koso (1998), 43(16), 2503-2509
CODEN: TAKKAJ; ISSN: 0039-9450
PB Kyoritsu Shuppan
DT Journal; General Review
LA Japanese
AB A review with 33 refs. on suppression of cytotoxic T cell and natural killer cell by ISP-1, inhibition of serine palmitoyltransferase and sphingolipid formation, induction of apoptosis by ISP-1, and cloning of ISP-1-resistant gene in yeast.

L8 ANSWER 30 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1996:400740 CAPLUS
DN 125:157601
TI "Sphingosine pathway". A novel apoptosis inducting pathway
AU Kozutsumi, Yasunori; Nakamura, Sachiko; Kawasaki, Toshisuke
CS Fac. Pharm. Sci., Kyoto Univ., Kyoto, 606, Japan

SO Seikagaku (1996), 68(6), 444-452
CODEN: SEIKAQ; ISSN: 0037-1017
PB Nippon Seikagakkai
DT Journal; General Review
LA Japanese
AB A review with 41 refs., on the sphingosine-involved signaling of apoptosis induction elucidated by the study of action mechanism of immunosuppressant ISP-1, discussing discovery of ISP-1 from Isalia sinclairii, immunosuppressive mechanism of ISP-1, induction of delayed reproductive apoptosis, ISP-1-induced decrease of sphingolipids as trigger of apoptosis, proposition of sphingosine signaling pathway inducing apoptosis, cell-specificity of apoptosis induction by sphingosine pathway, and structure-activity relationships of ISP-1 and preparation of FTY720 intended for clin. application.

L8 ANSWER 31 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1996:54790 CAPLUS
DN 124:115361
TI Dual roles of sphingolipids in signaling of the escape from the onset of apoptosis in a mouse cytotoxic T-cell line, CTLL-2
AU Nakamura, Sachiko; Kozutsumi, Yasunori; Sun, Yidi; Miyake, Yurika; Fujita, Tetsuro; Kawasaki, Toshisuke
CS Dep. Biol. Chem., Kyoto Univ., Kyoto, 606, Japan
SO Journal of Biological Chemistry (1996), 271(3), 1255-7
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB In our previous study, the sphingosine-like immunosuppressant, ISP-1, was found to suppress the proliferation of an interleukin-2-dependent cytotoxic T cell line, CTLL-2, through the inhibition of serine palmitoyltransferase, which catalyzes the committed step of sphingolipid biosynthesis. Anal. of the effect of ISP-1 by flow cytometry revealed that the ISP-1-dependent decrease in cell number was not due to inhibition of the cell cycle progression of CTLL-2 cells but to the induction of apoptosis of the cells. The ISP-1-induced apoptosis was inhibited by the addition of sphingosine (2 μM), suggesting that this ISP-1-induced apoptosis is triggered by the decrease in the intracellular levels of sphingolipids caused by the inhibition of serine palmitoyltransferase. However, another interleukin-2-dependent cell line, F7, which was derived from a mouse pro-B cell line, did not show ISP-1-dependent apoptosis, indicating that the effect of ISP-1 may be specific for a certain type of T cell lineage such as CTLL-2. On the other hand, a high dose of sphingosine (5 μM) by itself induced the apoptosis of CTLL-2 cells. This sphingosine-dependent apoptosis was also observed with F7 cells. These results provide evidence that the intracellular levels of sphingolipids play an important role in the signaling of the escape from and onset of apoptosis of CTLL-2 cells.

L8 ANSWER 32 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1995:634267 CAPLUS
DN 123:102274
TI Serine palmitoyltransferase is the primary target of a sphingosine-like immunosuppressant, ISP-1/myriocin
AU Miyake, Yurika; Kozutsumi, Yasunori; Nakamura, Sachiko; Fujita, Tetsuro; Kawasaki, Toshisuke
CS Dep. Biol. Chem., Fac. Pharmaceutical Sci., Kyoto Univ., Kyoto, 606, Japan
SO Biochemical and Biophysical Research Communications (1995), 211(2), 396-403
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic
DT Journal
LA English
AB ISP-1/myriocin is a new type of remarkably potent immunosuppressant, the

structure of which is homologous to sphingosine. ISP-1/myriocin inhibited the proliferation of an IL-2-dependent mouse cytotoxic T cell line, CTLL-2, at nanomole concns. ISP-1/myriocin inhibits serine palmitoyltransferase activity at picomole concns. This enzyme catalyzes the first step of sphingolipid biosynthesis and reduces the intracellular pool of sphingolipid intermediates. The growth inhibition induced by ISP-1/myriocin was completely abolished by the addition of sphingosines or sphingosine-1-phosphate, but not by sphingomyelin or glycosphingolipids. These results suggest that sphingosines or sphingosine-1-phosphate are associated with CTLL-2 proliferation, and ISP-1/myriocin suppresses T cell proliferation by the modulation of sphingolipid metabolism ISP-1/myriocin should be a useful tool for the study of the sphingolipid pathway, which has been associated with various kinds of signal transduction.

L8 ANSWER 33 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1994:212191 CAPLUS
DN 120:212191
TI Fungal metabolites. Part II. A potent immunosuppressive activity found in Isaria sinclairii metabolite
AU Fujita, Tetsuro; Inoue, Kenichiro; Yamamoto, Satoshi; Ikumoto, Takeshi; Sasaki, Shigeo; Toyama, Ryousuke; Chiba, Kenji; Hoshino, Yukio; Okumoto, Takeki
CS Fac. Pharm. Sci., Kyoto Univ., Kyoto, 606-01, Japan
SO Journal of Antibiotics (1994), 47(2), 208-15
CODEN: JANTAJ; ISSN: 0021-8820
DT Journal
LA English
AB A potent immunosuppressive activity was found in the culture broth of the fungus Isaria sinclairii (ATCC 24400). The metabolite, ISP-I [(2S,3R,4R)-(E)-2-amino-3,4-dihydroxy-2-hydroxymethyl-14-oxoeicos-6-enoic acid], suppressed the proliferation of lymphocytes in a mouse allogeneic mixed lymphocyte reaction, but had no effect on the growth of human tumor cell lines. It also suppressed the appearance of plaque-forming cells in response to sheep red blood cells and the generation of allo-reactive cytotoxic T lymphocytes in mice after i.p. or oral administration. The metabolite was 10-100-fold more potent than cyclosporin A as an immunosuppressive agent of the immune response in vitro and in vivo, and appears to be a candidate for clin. application as a powerful immunosuppressant.

L8 ANSWER 34 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1992:625544 CAPLUS
DN 117:225544
TI Inhibition of cytotoxic T lymphocytes induction by Isaria sinclairii-derived immunosuppressant, ISP-I
AU Chiba, Kenji; Hoshino, Yukio; Fujita, Tetsuro
CS Tokyo Res. Lab., Yoshitomi Pharm. Ind., Ltd., Tokyo, Japan
SO Cell (Tokyo, Japan) (1992), 24(5), 212-16
CODEN: SAIBD8; ISSN: 0386-4766
DT Journal; General Review
LA Japanese
AB A review, with 18 refs., on biol. activities of I. sinclairii-derived immunosuppressant, ISP-I (I), discussing the inhibitory actions of I on mixed lymphocyte reaction, cytotoxic T lymphocyte induction, and cytokine-dependent T lymphocyte differentiation, and comparison of action mechanism of I to that of cyclosporin A.

L8 ANSWER 35 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1974:78748 CAPLUS
DN 80:78748
TI Mechanism of action of the antifungal antibiotic thermozymocidin
AU Manachini, P. L.; Aragozzini, F.
CS Microbiol. Ind., Univ. Milano, Milan, Italy
SO Annali di Microbiologia ed Enzimologia (1972), 22(1-4), 55-62
CODEN: AMEZAB; ISSN: 0003-4649

DT Journal
LA Italian
AB Thermozymocidin [37836-36-5], an antifungal antibiotic having the structure of an α-hydroxymethyl-α-amino acid, inhibited the growth of submerged cultures of Saccharomyces cerevisiae at 0.5 μg/ml. At this concentration, inhibition of cell budding and a reduction in cell size occurred. The anaerobic and aerobic metabolism of glucose was not affected. Cell contents of RNA and protein were not altered, whereas a marked increase in DNA content and a decrease in nonprotein N were observed

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	164.25	176.34

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-31.20	-31.20

FILE 'STNGUIDE' ENTERED AT 07:45:08 ON 20 APR 2007
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Apr 13, 2007 (20070413/UP).

=>
=> s l2 and ceramide
'RN' IS NOT A VALID FIELD CODE
0 35891-70-4/RN
0 CERAMIDE
L9 0 L2 AND CERAMIDE

=> s 35891-70-4/rn
'RN' IS NOT A VALID FIELD CODE
L10 0 35891-70-4/RN

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	2.16	178.50

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-31.20

FILE 'CAPLUS' ENTERED AT 08:06:26 ON 20 APR 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1907 - 20 Apr 2007 VOL 146 ISS 18
FILE LAST UPDATED: 19 Apr 2007 (20070419/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html

=> s 35891-70-4/rn
107 35891-70-4
4 35891-70-4D
L11 103 35891-70-4/RN
(35891-70-4 (NOTL) 35891-70-4D)

=> s l11 and ceramide
9632 CERAMIDE
L12 17 L11 AND CERAMIDE

=> d 1-17 bib abs

L12 ANSWER 1 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2007:359961 CAPLUS
DN 146:330515
TI Inhibition of ceramide synthesis ameliorates glucocorticoid-, saturated-fat-, and obesity-induced insulin resistance
AU Holland, William L.; Brozinick, Joseph T.; Wang, Li-Ping; Hawkins, Eric D.; Sargent, Katherine M.; Liu, Yanqi; Narra, Krishna; Hoehn, Kyle L.; Knotts, Trina A.; Siesky, Angela; Nelson, Don H.; Karathanasis, Sotirios K.; Fontenot, Greg K.; Birnbaum, Morris J.; Summers, Scott A.
CS Division of Endocrinology, Metabolism, and Diabetes, Department of Internal Medicine, University of Utah, Salt Lake City, UT, 84132, USA
SO Cell Metabolism (2007), 5(3), 167-179
CODEN: CMEEB5; ISSN: 1550-4131
PB Cell Press
DT Journal
LA English
AB Insulin resistance occurs in 20% - 25% of the human population, and the condition is a chief component of type 2 diabetes mellitus and a risk factor for cardiovascular disease and certain forms of cancer. Herein, we demonstrate that the sphingolipid ceramide is a common mol. intermediate linking several different pathol. metabolic stresses (i.e., glucocorticoids and saturated fats, but not unsatd. fats) to the induction of insulin resistance. Moreover, inhibition of ceramide synthesis markedly improves glucose tolerance and prevents the onset of frank diabetes in obese rodents. Collectively, these data have two important implications. First, they indicate that different fatty acids induce insulin resistance by distinct mechanisms discerned by their reliance on sphingolipid synthesis. Second, they identify enzymes required for ceramide synthesis as therapeutic targets for combating insulin resistance caused by nutrient excess or glucocorticoid therapy.
RE.CNT 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2007:152773 CAPLUS
DN 146:352810
TI Expression, activity, and role of serine palmitoyltransferase in the rat hippocampus after kainate injury
AU He, Xin; Guan, Xue-Li; Ong, Wei-Yi; Farooqui, Akhlaq A.; Wenk, Markus R.
CS Department of Anatomy, National University of Singapore, Singapore, Singapore
SO Journal of Neuroscience Research (2007), 85(2), 423-432
CODEN: JNREDK; ISSN: 0360-4012
PB Wiley-Liss, Inc.
DT Journal

LA English
AB An increase in ceramide species was shown recently by lipid anal. of the rat hippocampus after kainate-induced excitotoxic injury. In this study, the authors showed increased expression of serine palmitoyltransferase (SPT), the 1st enzyme in the ceramide biosynthetic pathway, in reactive astrocytes of the hippocampus after kainate injections. The increase in enzyme expression was paralleled by increased SPT enzyme activity in the hippocampus at 2 wk post-kainate injection. In vitro studies showed that treatment of hippocampal slice cultures with SPT inhibitor ISP-1 (myriocin) or L-cycloserine modulated increases in 16:0, 18:0, and 20:0 ceramide species, and partially reduced kainate-induced cell death. The above findings indicate a role of SPT in ceramide increase after kainate injury, although addnl. effects of sphingomyelinase cannot be ruled out. They also suggest that SPT activity might contribute to neuronal injury after kainate excitotoxicity.
RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:152763 CAPLUS
DN 144:226248
TI Drug for treating or preventing HCV infection
IN Sudo, Masayuki; Sakamoto, Hiroshi
PA Chugai Seiyaku Kabushiki Kaisha, Japan
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2006016657	A1	20060216	WO 2005-JP14767	20050811

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRAI JP 2004-234900 A 20040811
OS MARPAT 144:226248
AB By discussing the HCV replicon inhibitory activities of compds. originating in microorganisms such as one belonging to the genus Aureobasidium, myriocin, fumonisin B1 and a ceramide transportation inhibitor HPA-12, it is observed that these compds. have effects of inhibiting the replication of HCV replicon RNA or inhibiting the expression of the HCV protein. By performing a knockdown experiment on serine palmitoyl transferase with the use of siRNA, it is found out that the HCV replicon activity and the expression of the HCV protein are significantly inhibited in cells wherein the expression of LCB1 is regulated, suggesting that sphingo lipid biosynthesis might participate in HCV infection. Based on these facts, it is clarified that HCV infection can be treated or prevented by inhibiting an enzyme activity occurring in the process of sphingo lipid biosynthesis by the addition of a compound or the knockdown of a gene.
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2005:953103 CAPLUS
DN 144:427181
TI Ethanol-Induced Changes in the Content of Triglycerides, Ceramides, and Glucosylceramides in Cultured Neurons
AU Saito, Mariko; Saito, Mitsuo; Cooper, Thomas B.; Vadasz, Csaba
CS Laboratory of Neurobehavior Genetics and the Division of Analytical Psychopharmacology, The Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, 10962, USA
SO Alcoholism: Clinical and Experimental Research (2005), 29(8), 1374-1383
CODEN: ACRSDM; ISSN: 0145-6008
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Ethanol induces apoptosis in cultured neurons. To assess the involvement of sphingolipids and neutral lipids in the apoptotic process, ethanol-induced alterations in lipid content and metabolism were examined by using primary cultured rat cerebellar granule neurons (CGNs), human neuroblastoma SK-N-SH cells, and mouse neuroblastoma Neuro2a cells. Ethanol treatment conditions that induced apoptosis in CGNs and SK-N-SH cells but not in Neuro2A cells were used for these expts. Cultured neurons were treated with and without 100 mM ethanol for 1-3 days, and the amts. of cellular sphingolipids [ceramide, glucosylceramide (GlcCer), and sphingomyelin] and neutral lipids [cholesterol, triglyceride (TG), and cholesterol ester (ChE)] were analyzed by high-performance thin-layer chromatog., using a Coomassie brilliant blue staining method. The incorporation of [C] acetate into each lipid fraction was measured in CGNs treated with and without ethanol. Also, the effect of delipidated serum, sterols, myriocin (a serine-palmitoyltransferase inhibitor), and desipramine (an acid sphingomyelinase inhibitor) on ethanol-induced lipid changes was studied by using Neuro2A cells. The most prominent change common to CGN, SK-N-SH, and Neuro2A cells was ethanol-induced TG accumulation. Higher incorporation of radioactivity into TG was also observed in ethanol-treated cultures when cellular lipids were metabolically labeled with [C] acetate in CGNs. In addition, ethanol elevated ceramide levels in all these neurons. However, ethanol induced decreases in GlcCer along with the reduction of cell viability in SK-N-SH cells and CGNs, whereas it increased GlcCer in Neuro2A cells that remained viable. Myriocin, which reduced ceramide levels, attenuated ethanol-induced cell death in SK-N-SH cells. Ethanol-induced accumulation of TG was sterol-independent, whereas changes in ceramide and GlcCer were affected in Neuro2A cells by the presence of sterols in the medium. Staurosporine, which induced cell death in SK-N-SH cells, increased levels of TG, ChE, and ceramides and reduced the level of GlcCer. The results showing that ethanol induces the accumulation of TG and ceramide in cultured neurons suggest that ethanol enhances lipogenesis and(or) reduces fatty acid degradation in neurons, as previously observed in other cell types. Further, ethanol-induced changes in lipid metabolism, specifically those of ceramide and GlcCer, may be related to the ethanol-induced apoptotic pathway.
RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:823310 CAPLUS
DN 143:206468
TI Ceramide de novo synthesis-based methods for modulation of mature SREBP, and related therapeutic methods and articles of manufacture
IN Worgall, Tilla S.; Deckelbaum, Richard J.
PA USA
SO U.S. Pat. Appl. Publ., 45 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI	US 2005182020	A1	20050818	US 2003-712684	20031114
PRAI	US 2003-712684		20031114		

AB A method is described for decreasing the amount of mature SREBP (mSREBP) in a cell characterized by an elevated level of mSREBP comprising contacting the cell with an agent that specifically inhibits de novo synthesis of ceramide in the cell, thereby decreasing the amount of mSREBP in the cell. Also described are related therapeutic methods and articles of manufacture

L12 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:326221 CAPLUS
DN 142:458423
TI Myriocin prevents fumonisin B1-induced sphingoid base accumulation in mice liver without ameliorating hepatotoxicity
AU He, Quanren; Riley, Ronald T.; Sharma, Raghubir P.
CS Department of Physiology and Pharmacology, College of Veterinary Medicine, University of Georgia, Athens, GA, 30602-7389, USA
SO Food and Chemical Toxicology (2005), 43(6), 969-979
CODEN: FCTOD7; ISSN: 0278-6915
PB Elsevier B.V.
DT Journal
LA English
AB Fumonisin B1 (FB1), a mycotoxin produced by Fusarium verticillioides present on corn and corn-based products, causes species- and organ-specific diseases. The hepatotoxic effects of FB1 in mice were closely correlated with the accumulation of free sphinganine, a marker for ceramide synthase inhibition, and reduced biosynthesis of more complex sphingolipids. It was shown that FB1 modulates expression of many cell signaling factors. In the current study the authors used myriocin, a specific inhibitor of serine palmitoyltransferase, to investigate the role of free sphinganine accumulation in FB1-induced hepatotoxicity and increased expression of selected signaling genes in BALB/c mice. The mice were pretreated daily with i.p. injection of 1.0 mg/kg myriocin 30 min before s.c. injections of 2.25 mg/kg of FB1 for 3 days. Results showed that myriocin alone was not hepatotoxic and the combination of myriocin plus FB1 completely prevented the FB1-induced elevation of hepatic free sphinganine and prevented the FB1-induced induction of selected cell signaling genes, suggesting that accumulation of free sphinganine and/or its metabolites contribute to the FB1-modulation of the cell signaling factors. However, the combination of myriocin and FB1 did not prevent FB1-increased concentration of plasma alanine aminotransferase and only slightly attenuated aspartate aminotransferase; it did not affect the FB1-induced hepatocyte apoptosis or increased cell proliferation. A longer combined treatment of myriocin and FB1 was highly toxic. The hepatotoxic effects in mice seen in this study are most likely due to a combination of factors including accumulation of free sphinganine, depletion of more complex sphingolipids and sphingomyelin, or other unknown mechanisms.
RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:223797 CAPLUS
DN 142:385619
TI Effect of Myriocin on Plasma Sphingolipid Metabolism and Atherosclerosis in apoE-deficient Mice
AU Hojjati, Mohammad Reza; Li, Zhiqiang; Zhou, Hongwen; Tang, Songshan; Huan, Chongmin; Ooi, Everlyn; Lu, Shendi; Jiang, Xian-Cheng
CS Department of Anatomy and Cell Biology, State University of New York Downstate Medical Center, Brooklyn, NY, 11203, USA
SO Journal of Biological Chemistry (2005), 280(11), 10284-10289
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal

LA English
AB Sphingolipids play a very important role in cell membrane formation, signal transduction, and plasma lipoprotein metabolism, all of which may well have an impact on the development of atherosclerosis. To investigate the relationship between sphingolipid metabolism and atherosclerosis, we utilized myriocin to inhibit mouse serine palmitoyl-CoA transferase (SPT), the key enzyme for sphingolipid biosynthesis. We injected 8-wk-old apoE-deficient mice with myriocin (0.3 mg/kg/every other day, i.p.) for 60 days. On a chow diet, myriocin treatment caused a significant decrease (50%) in liver SPT activity ($p < 0.001$), significant decreases in plasma sphingomyelin, ceramide, and sphingosine-1-phosphate levels (54, 32, and 73%, resp.) ($p < 0.0001$), and a significant increase in plasma phosphatidylcholine levels (91%) ($p < 0.0001$). Plasma total cholesterol and triglyceride levels demonstrated no significant changes, but there was a significant decrease in atherosclerotic lesion area (42% in root and 36% in en face assays) ($p < 0.01$). On a high fat diet, myriocin treatment caused marked decreases in plasma sphingomyelin, ceramide, and sphingosine-1-phosphate levels (59, 66, and 81%, resp.) ($p < 0.0001$), and a marked increase in plasma phosphatidylcholine levels (100%) ($p < 0.0001$). Total cholesterol and triglyceride demonstrated no significant changes, but there was a significant decrease in atherosclerotic lesion area (39% in root and 37% in en face assays) ($p < 0.01$). These results indicate that, apart from cholesterol levels, sphingolipids have an effect on atherosclerotic development and that SPT has proatherogenic properties. Thus, inhibition of SPT activity could be an alternative treatment for atherosclerosis.
RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 8 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:1057420 CAPLUS
DN 142:193189
TI Fungal Metabolite Sulfamisterin Suppresses Sphingolipid Synthesis through Inhibition of Serine Palmitoyltransferase
AU Yamaji-Hasegawa, Akiko; Takahashi, Atsushi; Tetsuka, Yasuyuki; Senoh, Yukiko; Kobayashi, Toshihide
CS RIKEN, Wako, Saitama, 351-0198, Japan
SO Biochemistry (2005), 44(1), 268-277
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
OS CASREACT 142:193189
AB Sphingolipids and their metabolites are known to modulate various cellular events including proliferation, differentiation, and apoptosis. Serine palmitoyltransferase (SPT) is the enzyme that catalyzes the first step of the biosynthesis of all sphingolipids. Here, we report that a newly identified antibiotic, sulfamisterin, derived from the fungus Pycnidiella sp., is a specific inhibitor of SPT. The chemical structure of sulfamisterin resembles both that of sphingosine as well as a potent inhibitor of SPT, ISP-1 (myriocin). Sulfamisterin inhibited SPT activity with IC50 = 3 nM in a cell-free lysate prepared from Chinese hamster ovary (CHO) fibroblasts. Sulfamisterin markedly inhibited the biosynthesis of sphingolipids in living CHO cells and in yeast Saccharomyces cerevisiae as monitored by radioactive precursors. Unlike the cell-free expts., 10 μM sulfamisterin was required for complete inhibition of sphingolipid biosynthesis in intact cells. We also synthesized a series of structural analogs of sulfamisterin and examined their activities both in cell-free and in living cell systems.
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:947989 CAPLUS
DN 142:232571

TI Fenretinide stimulates redox-sensitive ceramide production in breast cancer cells: potential role in drug-induced cytotoxicity
AU Rehman, F.; Shanmugasundaram, P.; Schrey, M. P.
CS Imperial College London, Section of Endocrinology & Metabolic Medicine, St Mary's Hospital, London, W2 1NY, UK
SO British Journal of Cancer (2004), 91(10), 1821-1828
CODEN: BJCAAI; ISSN: 0007-0920
PB Nature Publishing Group
DT Journal
LA English
AB The synthetic retinoid N-(4-hydroxphenyl) retinamide (4HPR) has manifold actions, which may contribute to its chemopreventive effects on breast cancer cell growth and progression. A role for ceramide as a stress-response signal is investigated here during the cytotoxic action of 4HPR in MCF-7 cells. N-(4-hydroxphenyl) retinamide induced a dose-dependent decline in cell growth and survival associated with a maximal 10-fold increase in ceramide production at 10 μM. N-(4-hydroxphenyl) retinamide exhibited a greater potency than all-trans retinoic acid (ATRA) on growth inhibition and ceramide production The synthetic peroxisome proliferator-activated receptors agonist troglitazone (TGZ), but not the native ligand 15-deoxy-delta 12,14-prostaglandin J2, abrogated both these actions of 4HPR but not that of ATRA. The antioxidant N-acetylcysteine mimicked the abrogative effect of TGZ on 4HPR action, while the exogenous oxidant H2O2 also stimulated ceramide production The inhibitors of de novo ceramide synthesis, fumonisin B1 and myriocin, blocked the ceramide response to 4HPR and partially reversed the apoptotic response, but did not prevent the overall decline in cell survival. The pancaspase inhibitor Z-VAD fmk reduced the decrease in cell survival caused by 4HPR, but did not affect the ceramide response. These findings describe a novel redox-sensitive elevation of ceramide levels associated with the cytotoxic response of breast cancer cells to 4HPR. However, a major mediatory role for this sphingolipid in this context remains equivocal.
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 10 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:875226 CAPLUS
DN 142:50573
TI Altered de novo sphingolipid biosynthesis is involved in the serum deprivation-induced cell death in LLC-PK1 cells
AU Yu, Min; Yoo, Jae; Lee, Youn; Lee, Yong; Hong, Jin; Oh, Ki; Song, Sukgil; Yun, Yeo; Yoo, Hwan; Oh, Sei
CS College of Pharmacy, Chungbuk National University, Cheongju, S. Korea
SO Journal of Toxicology and Environmental Health, Part A (2004), 67(23-24), 2085-2094
CODEN: JTEHF8; ISSN: 1528-7394
PB Taylor & Francis, Inc.
DT Journal
LA English
AB Fumonisin B1, a specific inhibitor of ceramide synthase, and ISPI (Myriocin), a serine palmitoyltransferase inhibitor, modulate the de novo sphingolipid biosynthesis pathway. This study was conducted to determine whether serum deprivation-induced cell death is regulated by de novo sphingolipid biosynthesis in pig kidney LLC-PK1 cells. Serum withdrawal from the culture medium produced cell death in LLC-PK1 cells. Fumonisin B1 at concns. ranging from 5μM to 30μM delayed until 48 h this cell death resulting from the absence of fetal bovine serum (FBS) in cell culture. Pretreatment of cultured cells with fumonisin B1 in the presence of serum for 24 h increased by approx. 70% this cytoprotective activity of fumonisin B1 against serum deprivation-induced cell death. Serum deprivation increased sphingolipid biosynthesis threefold compared to 5% serum-enriched culture. Fumonisin B1 at 5-30 μM lowered the content of total complex sphingolipids to levels of 50% and 77% of the content in

serum-enriched culture, although the concentration of intracellular free sphinganine was elevated. ISPI alone at greater than 1 nMconcn. reduced total complex sphingolipid content to values in LLC-PK1 cells grown in the presence of 5% FBS. The results suggest that the de novo complex sphingolipid biosynthesis modulated by either fumonisin B1 or ISPI may regulate serum deprivation-induced cell death in LLC-PK1 cells.

RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:436444 CAPLUS
DN 141:388255
TI Resveratrol structure and ceramide-associated growth inhibition in prostate cancer cells
AU Sala, G.; Minutolo, F.; Macchia, M.; Sacchi, N.; Ghidoni, R.
CS Laboratory of Biochemistry and Molecular Biology, San Paolo University Hospital, School of Medicine, University of Milan, Italy
SO Drugs under Experimental and Clinical Research (2003), 29(5/6), 263-269
CODEN: DECRDP; ISSN: 0378-6501
PB Bioscience Ediprint Inc.
DT Journal
LA English
AB Resveratrol (3,4',5-trans-trihydroxystilbene) is a dietary polyphenol with chemopreventive properties present in grapes, red wine, peanuts and other edible products. The antiproliferative and proapoptotic effect of resveratrol in breast cancer cells can be traced to the accumulation of ceramide. In this study we demonstrate that resveratrol can also exert antiproliferative/proapoptotic effects in association with the accumulation of endogenous ceramide in the androgen receptor (AR)-neg. prostate cancer cell line, PC3. Notably, resveratrol shares with other ceramide-inducing agents a phenolic moiety on its structure. For this reason we hypothesize that the phenolic moiety is critical for the ceramide-associated growth-inhibitory effects of resveratrol. We compared the ability to induce both ceramide increase and growth inhibition in PC3 cells of resveratrol and three resveratrol analogs: piceatannol (3,3',4',5-trans-tetrahydroxystilbene), with an addnl. hydroxyl group in the 3' position; trans-stilbene, the nonhydroxylated analog; and the semisynthetic 3,4',5-trimethoxy-trans-stilbene (TmS), with methoxyl groups in lieu of the hydroxyl groups. Of the three stilbenoids, only piceatannol (and not stilbene or TmS) produced ceramide-associated growth inhibition. These data point to the phenolic moiety of stilbenoids as a critical structural feature necessary to induce ceramide-associated growth inhibition.

RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 12 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:848290 CAPLUS
DN 140:138915
TI Involvement of endogenous ceramide in the inhibition of telomerase activity and induction of morphologic differentiation in response to all-trans-retinoic acid in human neuroblastoma cells
AU Kraveka, Jacqueline M.; Li, Li; Bielawski, Jacek; Obeid, Lina M.; Ogretmen, Besim
CS Department of Pediatrics, Division of Hematology/Oncology, Medical University of South Carolina, Charleston, SC, 29425, USA
SO Archives of Biochemistry and Biophysics (2003), 419(2), 110-119
CODEN: ABBIA4; ISSN: 0003-9861
PB Elsevier Science
DT Journal
LA English
AB In this study, we examined the role of endogenous ceramide in the inhibition of telomerase and induction of morphol. differentiation in response to all-trans-retinoic acid (ATRA) in the SK-N-SH and SK-N-AS human neuroblastoma cell lines. The results showed that ATRA inhibited

the activity of telomerase significantly in a time- and dose-dependent manner, as determined by telomere repeat amplification protocol (TRAP). The inhibition of telomerase by ATRA was maximum (about 50-80% of untreated controls) at 5-10 μM for 4-8 days. Treatment of cells with ATRA (5 μM) also resulted in the inhibition of growth by about 30-70% after 4 and 8 days of treatment, resp., which was measured by trypan blue exclusion method. Measurement of accumulation of endogenous ceramide by high pressure liquid chromatog. coupled with mass spectroscopy (LC/MS) showed that treatment of cells with ATRA resulted in increased levels of mainly C24:0 and C24:1 ceramides at days 2, 4, and 8, resp. Also, treatment of cells with ATRA in the presence of myriocin blocked the accumulation of ceramide significantly, and more importantly, presence of myriocin partially prevented the inhibition of telomerase. Mechanistically, inhibition of telomerase by endogenous ceramide in response to ATRA treatment involves, at least in part, down-regulation of the expression of telomerase reverse transcriptase (hTERT) mRNA, as determined by semi-quant. RT-PCR, in these cells. In addition, the modulation of telomerase activity by ATRA correlated with the induction of morphol. differentiation, which was also blocked by myriocin, as determined by extension of neurites using phase-contrast microscopy. These results, therefore, reveal an important effect of ATRA on telomerase inhibition and induction of morphol. differentiation in human neuroblastoma cells. These data also demonstrate that endogenous ceramide is one of the upstream regulators of telomerase activity in human neuroblastoma cells in response to ATRA.

RE.CNT 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:952726 CAPLUS
DN 138:395628
TI Ceramide Signaling in Fenretinide-Induced Endothelial Cell Apoptosis
AU Erdreich-Epstein, Anat; Tran, Linda B.; Bowman, Nina N.; Wang, Hongtao; Cabot, Myles C.; Durden, Donald L.; Vlckova, Jitka; Reynolds, C. Patrick; Stins, Monique F.; Groshen, Susan; Millard, Melissa
CS Keck School of Medicine, Department of Pediatrics, Childrens Hospital Los Angeles, Division of Hematology-Oncology, University of Southern California, Los Angeles, CA, 90027, USA
SO Journal of Biological Chemistry (2002), 277(51), 49531-49537
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB Stress stimuli can mediate apoptosis by generation of the lipid second messenger, ceramide. Herein we investigate the mol. mechanism of ceramide signaling in endothelial apoptosis induced by fenretinide (N-(4-hydroxyphenyl)retinamide (4-HPR)). 4-HPR, a synthetic derivative of retinoic acid that induces ceramide in tumor cell lines, has been shown to have antiangiogenic effects, but the mol. mechanism of these is largely unknown. We report that 4-HPR was cytotoxic to endothelial cells (50% cytotoxicity at 2.4 μM, 90% at 5.36 μM) and induced a caspase-dependent endothelial apoptosis. 4-HPR (5 μM) increased ceramide levels in endothelial cells 5.3-fold, and the increase in ceramide was required to achieve the apoptotic effect of 4-HPR. The 4-HPR-induced increase in ceramide was suppressed by inhibitors of ceramide synthesis, fumonisin B1, myriocin, and L-cycloserine, and 4-HPR transiently activated serine palmitoyltransferase, demonstrating that 4-HPR induced de novo ceramide synthesis. Sphingomyelin levels were not altered by 4-HPR, and desipramine had no effect on ceramide level, suggesting that sphingomyelinase did not contribute to the 4-HPR-induced ceramide increase. Finally, the pancaspase inhibitor, t-butyloxycarbonyl-aspartyl[O-methyl]-fluoromethyl ketone, suppressed

4-HPR-mediated apoptosis but not ceramide accumulation, suggesting that ceramide is upstream of caspases. Our results provide the first evidence that increased ceramide biosynthesis is required for 4-HPR-induced endothelial apoptosis and present a mol. mechanism for its antiangiogenic effects.

RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:390534 CAPLUS
DN 136:381627
TI Pharmacological antagonism of fumonisin B1 cytotoxicity in porcine renal epithelial cells (LLC-PK1): A model for reducing fumonisin-induced nephrotoxicity in vivo
AU He, Quanren; Riley, Ronald T.; Sharma, Raghubir P.
CS Department of Physiology and Pharmacology, College of Veterinary Medicine, The University of Georgia, Athens, GA, 30602, USA
SO Pharmacology & Toxicology (Oxford, United Kingdom) (2002), 90(5), 268-277
CODEN: PHTOEH; ISSN: 0901-9928
PB Blackwell Publishers Ltd.
DT Journal
LA English
AB Fumonisin B1 is a mycotoxin commonly found on corn. It is hepatotoxic and nephrotoxic in domestic and exptl. animals, and causes equine leukoencephalomalacia and porcine pulmonary edema. It is a potent inhibitor of ceramide synthase. Inhibition leads to accumulation of free sphingoid bases in cells and tissues. In pig kidney epithelial cells (LLC-PK1), fumonisin B1 induces increased tumor necrosis factor α (TNFα) expression independent of the accumulation of sphingoid bases. The objective of this study was to investigate pharmacol. approaches for intervening in fumonisin B1 toxicity using the LLC-PK1 cell model. The toxicity of fumonisin B1 was assayed using cell viability and lactate dehydrogenase (lactate dehydrogenase) release. Pretreatment of cells with myriocin, preventing sphinganine accumulates, prevented the fumonisin B1-induced decrease in cell viability and increased lactate dehydrogenase release. Modulation of adenosine receptor activity did not reduce the fumonisin B1 cytotoxicity. As with myriocin, silymarin pretreatment prevented the fumonisin B1-induced effects on cell viability and lactate dehydrogenase release. When added 6 or 24 h after treatment of cells with fumonisin B1, both myriocin and silymarin reversed the decreased cell viability and suppressed the increased lactate dehydrogenase release. Myriocin, but not silymarin, blocked the accumulation of sphinganine in fumonisin B1-treated cells. Silymarin, unlike myriocin, induced expression of TNFα to an extent similar to fumonisin B1, but pretreatment with silymarin decreased the fumonisin B1-induced TNFα expression in LLC-PK1 cells. Results suggest that the mechanisms by which myriocin and silymarin protect renal cells are different, and silymarin potentially prevents fumonisin B1-induced toxicity by modulating TNFα expression or signals downstream of the inhibition of ceramide synthase.

RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 15 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2001:798090 CAPLUS
DN 135:341174
TI Detection and treatment of atherosclerosis based on plasma sphingomyelin concentration
IN Tall, Alan R.; Jiang, Xian-Cheng
PA Trustees of Columbia University in the City of New York, USA
SO PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001080903	A1	20011101	WO 2001-US12706	20010419
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
PRAI	US 2000-551947	A	20000419		

OS MARPAT 135:341174

AB The invention concerns new enzymic methods of plasma and tissue sphingomyelin concentration measurement. Also disclosed is that human plasma sphingomyelin levels are strongly pos. correlated with atherosclerosis and coronary heart disease. Thus, the use of a quick and effective plasma sphingomyelin measurement such as the subject invention, is valuable for screening assays in vitro, in cell culture or in animals to develop drugs or other treatments aimed to lower plasma sphingomyelin levels. The findings indicate that therapies aimed at reducing plasma or tissue SM levels are likely to have therapeutic benefit. These would include inhibition of sphingomyelin synthesis in the liver or arterial wall, as well as methods to enhance clearance of sphingomyelin from plasma. Thus, compds. which inhibit sphingomyelin biosynthesis or induce sphingomyelin clearance are also disclosed.

L12 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2001:43127 CAPLUS

DN 134:203534

TI Alteration in sphingolipid metabolism: Bioassays for fumonisin- and ISP-I-like activity in tissues, cells and other matrices

AU Riley, R. T.; Norred, W. P.; Wang, E.; Merrill, A. H.

CS Toxicology and Mycotoxin Research Unit, Athens, GA, 30604-5677, USA

SO Natural Toxins (1999), 7(6), 407-414
CODEN: NATOEE; ISSN: 1056-9014

PB John Wiley & Sons Ltd.

DT Journal

LA English

AB The first discovered naturally occurring inhibitor of de novo sphingolipid biosynthesis was fumonisin B1. There are now 11 identified fungal inhibitors of ceramide synthase or 'fumonisin B1-like' compds. With the exception of the australifungins, all other fungal ceramide synthase inhibitors are structurally sphingoid-like. There are several recently discovered fungal inhibitors of another enzyme in the de novo sphingolipid biosynthesis pathway: serine palmitoyltransferase (SPT). One of the SPT inhibitors is named ISP-I. While ceramide synthase inhibitors are toxic to animals, plants and fungi, the SPT inhibitors are not known to cause animal or plant disease, but are potent inhibitors of fungal growth. Very little is known about their toxicity in animals. There are at least 24 fungal SPT inhibitors produced by a variety of fungi. Given that the fungal inhibitors of sphingolipid biosynthesis are chemical and biol. diverse, two bioassays have been developed to screen for fumonisin-like or ISP-I-like activity in naturally contaminated products or fungal culture materials. These bioassays are based on the changes in free sphingoid base concentration that occur when the ceramide synthase or SPT are inhibited. The bioassays have the advantage that they are functionally rather than chemical specific and thus will detect ceramide synthase and SPT inhibitors regardless of their chemical structure.

RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 17 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN

AN 1999:464778 CAPLUS
DN 131:239004
TI Serine palmitoyltransferase inhibition reverses anti-proliferative effects of ceramide synthase inhibition in cultured renal cells and suppresses free sphingoid base accumulation in kidney of BALBc mice
AU Riley, Ronald T.; Voss, Kenneth A.; Norred, William P.; Bacon, Charles W.; Meredith, Filmore I.; Sharma, Raghubir P.
CS Toxicology and Mycotoxin Research Unit, Agricultural Research Service, United States Department of Agriculture, Athens, GA, USA
SO Environmental Toxicology and Pharmacology (1999), 7(2), 109-118
CODEN: ETOPFR; ISSN: 1382-6689
PB Elsevier Science B.V.
DT Journal
LA English
AB The purpose of this study was to determine the ability of the fungal serine palmitoyltransferase (SPT) inhibitor, myriocin, to prevent the anti-proliferative and cytotoxic effects of fumonisin B1 in cultured pig kidney epithelial cells, LLC-PK1. In an earlier study with LLC-PK1 cells, β-chloroalanine (a nonspecific SPT inhibitor) was found to inhibit the fumonisin-induced accumulation of free sphinganine by 90% but only partially reversed (50-60%) fumonisin's antiproliferative and cytotoxic effects. β-Chloroalanine is not the ideal SPT inhibitor for this type of study because it also inhibits other pyridoxal 5'-phosphate-dependent enzymes. A potent and selective fungal SPT inhibitor (myriocin) was partially purified from liquid cultures of Isaria (=Cordyceps) sinclairii by a combination of organic extraction and column chromatog. The various fractions were bioassayed for their ability to inhibit fumonisin-induced sphinganine accumulation in LLC-PK1 cells. The activity in partially purified material was compared to the activity of highly purified myriocin and the results expressed as myriocin equivalent The estimated IC50 and IC95 for inhibition of fumonisin-induced sphinganine accumulation were approx. 1.8 and 22 nM, resp. The IC95 concentration of the fungal SPT inhibitor reversed the antiproliferative effects and prevented fumonisin-induced apoptosis after 48 h exposure to 50 μM fumonisin B1. The SPT inhibitor was also effective at reducing free sphinganine in vivo. Free sphinganine concentration was reduced 60% in kidney of mice injected i.p. with SPT inhibitor plus fumonisin B1 when compared to fumonisin B1 alone. The ability of SPT inhibition to reduce fumonisin B1-induced sphinganine accumulation in vivo may be useful in the development of therapeutic agents for treatment of animals suspected to have been exposed to toxic levels of fumonisin in feeds.
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	54.61	233.11

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-13.26	-44.46

FILE 'STNGUIDE' ENTERED AT 08:06:56 ON 20 APR 2007

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Apr 13, 2007 (20070413/UP).

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.26	234.37

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-44.46

STN INTERNATIONAL LOGOFF AT 08:19:23 ON 20 APR 2007